# CHEMICAL AND PHYSICAL MODIFICATIONS OF ELECTROSPUN FIBERS AS A METHOD TO STIMULATE TISSUE REGENERATION – MINIREVIEW

**Roksana Kurpanik*, Ewa Stodolak-Zych***

AGH University of Science and Technology,
Faculty of Materials Science and Ceramics,
Department of Biomaterials and Composites,
Al. Mickiewicza 30, 30-059 Krakow, Poland
*e-mail: kurpanik@agh.edu.pl, stodolak@agh.edu.pl

## Abstract

*Fibrous scaffolds based on (bio)polymers are observed as mimicking the microstructure of the extracellular matrix. Thus, they are considered as an example of a utilitarian scaffold, useful for the regeneration of various types of tissues. The techniques described in the literature are well known to obtain submicrometric and nanometric fibers that, when randomly arranged, mimic the ECM.*

*The biomimetic scaffold criterion might be even better reflected if the cell adhesion sites are present on the surface of such fibers. They promote the formation of the focal adhesion contact or facilitate the formation of a protein film on the fiber surface. Such a process is enhanced by an appropriate physical or chemical modification that activates the protein adsorption and the subsequent cell adhesion. The aim of this paper is to present different methods of physical and/or chemical modifications of fibrous materials: which can serve as scaffolds to support the regeneration processes of various tissues. In terms of physical methods, only weak interactions between the surface and the modifier were observed. This technique is simple but not durable. Chemisorption used as a second method of fiber modification is possible if a covalent or ionic bond is formed between the fiber and the modifier. Therefore, the chemical adsorption may not be fully reversible and requires a sequence of chemical actions to form a chemical bond. The most commonly used methods are the combined methods where the first step is the physical activation of the fiber surface, which facilitates the chemical modification step.*

***Keywords:*** *electrospun fibers, fibrous scaffold, surface modification, extracellular matrix*

***[Engineering of Biomaterials 159 (2021) 31-41]***

***doi:10.34821/eng.biomat.159.2021.31-41***

## Introduction

The main purpose of the scaffold-based approach is not just to replace the missing tissue but also to create a microenvironment for its regeneration and, eventually, restoring its function. It could be achieved by a geometry which guarantees appropriate mechanical support and advantageous surface properties triggering cellular responses. The structure within the body responsible for these processes is the extracellular matrix (ECM) which is a three-dimensional mesh of macromolecules, such as collagen, glycoproteins, and enzymes [1]. The characteristic ECM structure provides the structural support for growing tissue, it induces the cell adhesion, migration and proliferation and affects its antibacterial properties. Therefore, the focus of tissue engineering is on mimicking the microstructure of the native extracellular matrix as well as its chemical activity.

Since the ECM is a permanent and unique part of every tissue in the human body, fibrous morphology is the most desired form of a scaffold for regenerative engineering. Research shows that the synergistic effect of the matrix composition, its architecture and stiffness play a big role in maintaining the tissue functions. The appropriate adjustment of its characteristic features at microstructural and structural level increases the chances of inducing regenerative processes [2]. Another study highlighted the importance of the surface topography in gene expression regulation. It revealed that fibrous microstructure has a greater potential for altering the human mesenchymal stem cells (hMSC) gene expression than a flat one [3]. It is reported that factors, such as the fiber diameter, porosity and the way they are organized, regulate the cells behaviour, especially their proliferation and differentiation. Finer PCL fibers ($\varnothing$ = 0.35 μm) promote the better differentiation of pre-osteoblastic cells (i.e. MC3T3-E1) while a larger diameter ($\varnothing$ = 6.5 μm) fibers exhibit the better proliferation [4]. Another study conducted by Lekshmi Krishna et al. also highlighted the impact of a fiber diameter on corneal epithelial cells (HCE-T) and the retinal pigment (ARPE-19). The research revealed that HCE-T seeded on PCL with a diameter of 500 nm exhibited the greater differentiation while those seeded on PCL with a diameter of 1300 nm showed the better proliferation. In the case of ARPE-19 cells seeded on larger fibers, the greater phagocytic activity and the lower apoptosis level were observed while on finer fibers the pluripotential behaviour and secretion of vascular endothelial growth factor A (VEGF-A) was higher [5].

There are lots of methods for ECM fibrillar structure restoration which include the phase separation technique, the molecular self-assembly and the electrospinning. Among them, the solution electrospinning is out of big interest because of its simplicity, the possibility of using various materials and generating nanoscale fibers with a high surface-to-volume ratio [6,7]. On the other hand, the use of a solvent increases the risk of the residual solvent remaining in the scaffold. Therefore, it may contribute to its toxicity towards the surrounding tissues and increase the production costs [8]. A method that does not involve a polymer solution is the melt electrospinning. In this technique, the fibers are formed directly by heating the polymer, therefore the disadvantages associated with the solvent application are eliminated, which, makes the melt electrospinning safe and green [8]. To reduce the fibers diameter, the process can be also aided by hot air (melt-blown electrospinning). By increasing the airflow velocity not only the fiber diameter is reduced but also its alignment and anisotropy are increased. It improves the Young Modulus and yield stress so the fibers are suitable for e.g. tendon regeneration [9,10]. The melt electrospinning writing is an additional manufacturing method that allows achieving aligned sub-micro- and microscale fibers (≈0.8 μm to ≈140 μm) [11]. The greater control over the fibers alignment ensures their arrangement into different shapes and obtaining the desired mechanical properties of a scaffold as well as the cellular alignment [11,12]. It is also proven that different geometric structures exhibit diverse drug release kinetics, which makes the melt electrospinning an attractive method for the wound dressing production [13].

The traditional electrospinning results in a two-dimensional microstructure and low porosity, which limits the cell migration within a scaffold. In the wet electrospinning, a metallic collector is replaced with a liquid solution, which enables achieving a three-dimensional, sponge-like microstructure that exhibits the improved porosity, hydrophilicity and cell adhesion and proliferation [14]. Another interesting technique for producing nanofibers is the rotary jet spinning (RJS). In this method, a polymer jet is ejected from the reservoir holes by a centrifugal force caused by the shaft rotation. Simultaneously, the solvent evaporates, therefore its low boiling point is necessary. Since the RJS uses the high-speed rotation instead of an electric field, a conductive solution is not required. This technique leads to aligned, submicrometric fibers with a rougher surface, in comparison to the electrospinning. Such a morphology limits the implant bacterial colonization without affecting the cell viability [15].

All the above-mentioned methods lead to obtaining scaffolds that differ in fibers dimensions, their arrangement, topography and porosity, including the diameters in the range of nanometers (<100 nm), sub-micrometers (<1 μm) and micrometers. The research shows that a scaffold consisting of both nano- and submicrometric fibers exhibits the most sufficient mechanical properties and cells penetration [16]. The diameter of the electrospun fibers differs from the collagen fibrils of the native ECM. However, the full functionality of the tissue is maintained also by a hierarchical microstructure of an extracellular matrix. Regardless of the type of tissue, this inhomogeneity plays a key role in maintaining homeostasis and inducing a cellular response and thus, it determines the proper regeneration and functionalization of the tissue. Therefore, there is a great demand for the substrates with a complex microstructure which allows for differentiation of the cells toward an appropriate phenotype, their infiltration into the scaffold and eventually the formation of the proper tissue. By changing the parameters of electrospinning it is possible to obtain fibers with different diameters, arrangements (aligned or randomly oriented) and morphology (smooth, porous, hollow, etc.). This diversity of nanofiber microstructure enables the control over the formation of a particular type of tissue. The fibers arrangement has also a big impact on the mechanical properties of the scaffold. Aligned fibers contribute to more anisotropic mechanical properties which are used in fibrous mats for bone and nerves regeneration [17,18]. The ability to mimic the morphology and composition of the ECM fibers is a reason behind the widespread use of electrospinning in biomedical applications. Unfortunately, the majority of synthetic electrospun fibers do not facilitate the cellular attachment due to the high hydrophobicity and inappropriate surface characteristics [19].

There are two ways of promoting the cells-scaffold interaction. The first one is a modification of the bulk material by the copolymers production, the piezoelectric materials application, and the plasma treatment of the pre-electrospinning solution, etc. [6,20]. The second way is the surface functionalization [20]. Both approaches facilitate the cell adhesion and antimicrobial behaviour of the scaffold by altering its surface morphology, roughness, hydrophilicity and free energy. However, the drawback of the first method is that any changes in the material's chemical composition may decrease its mechanical properties and thus its cell-supporting ability. Therefore, since the interactions between cells and scaffold occur at the interface, the promising strategy is to alter the surface properties, and not to modify the bulk material structure. Depending on the application, the surface characteristics requirements may vary but still there are a few that every scaffold must fulfil. These are: high biocompatibility, selective permeability, appropriate mechanical properties, antibacterial properties, lack of immunological response or cytotoxic behaviour [21,22]. Numerous technologies intended for fibers surface modification result in its various properties. All the methods derive from two long-known surface biofunctionalization strategies, i.e. physical and chemical modification (FIG. 1). The physical modification methods are simple, safe as well as cost and time efficient. However, the bond between the substrate and the coating material is not durable. On the other hand, chemical methods more closely reflect the conditions in the human body. They are also characterized by the higher durability, due to the new chemical bonds that appear between the fiber surface and the modifier. However, these methods are limited by the range of materials susceptible to chemical modifications. Since the aim of the ECM regeneration is to achieve the microstructural resemblance via the electrospinning, the challenge grows.

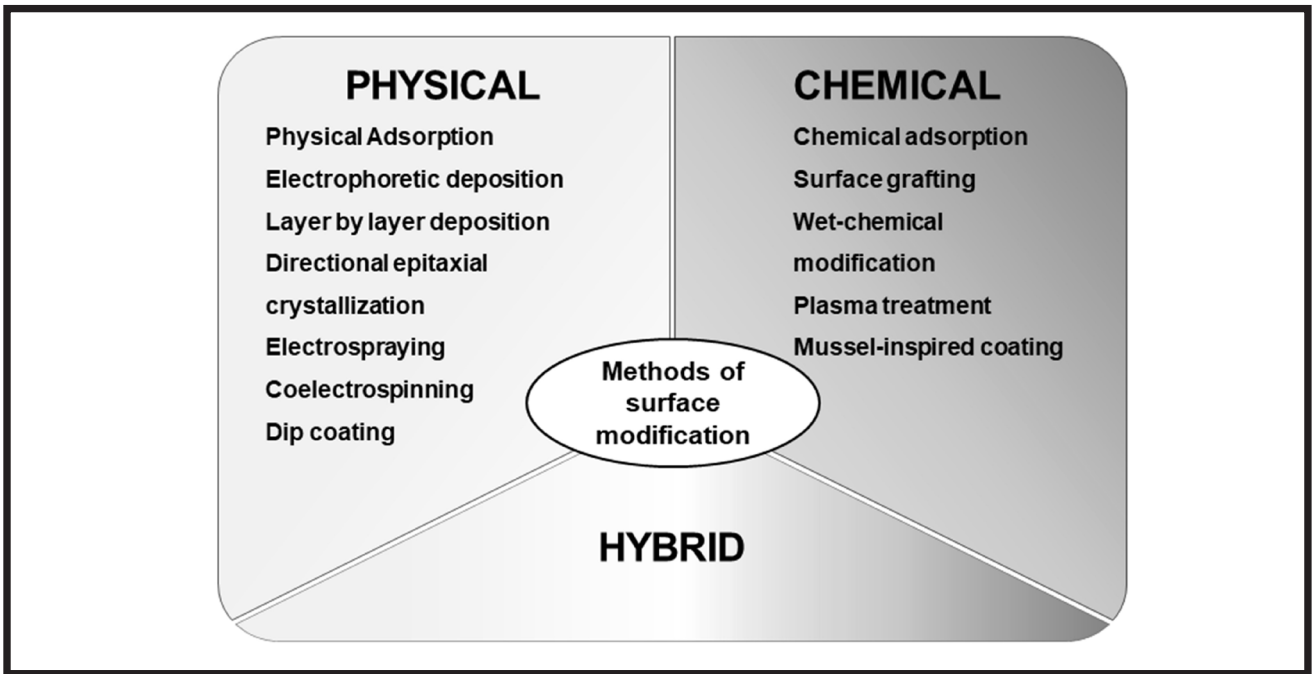


**FIG. 1. Methods of fibers surface modification.**

## Physical Surface Modification

Physical methods of modification belong to the simplest ways of immobilization. They are based on the physisorption characterized by weaker interactions between the substrate and an attached biomolecule, such as van der Waals forces, hydrogen bonding or hydrophobic interactions [23]. The following is a brief description of physical methods used in the literature to modify fibers. These include: the physical adsorption (immobilization), the electrophoretic deposition, the dip coating, the electrospraying, the co-electrospinning, the directional epitaxial crystallization, the layer by layer deposition.

### Physical Adsorption

The physical adsorption is the most commonly used technique because of its simplicity and the non-destructive character. It is based mainly on electrostatic interactions, such as hydrogen bonding or van der Waals forces between the substrate and the coating, without forming covalent bonds [24]. The main drawback of the physical adsorption is the random orientation of the molecules adsorbed on the surface, which may result in their functionality loss [25]. Chen et al. investigated the difference between the physical adsorption and the chemical treatment of silica/PVP composite fibers with laminin molecules. The outcomes indicated the covalent attachment as a better solution because the neural cells proliferation was significantly greater than that of the physically modified samples [26]. Jianhua Ye et al. modified the thermoplastic polyurethane surface by incorporating cellulose nanofibers (CNF) via the ultrasound-assisted method. The hydroxyl group of the adsorbed CNF improved the hydrophilicity and water retention ratio. It resulted in the better cell adhesion and proliferation, in comparison to the untreated polyurethane [4].

### Dip coating

Another physical surface modification method is the dip coating. It is simple, cost-effective and can be used even for complex geometries without wasting a lot of material. These advantages have contributed to its widespread use not only to produce scaffolds but also to modify the wettability and reduce the pore size of fibrous membranes [27]. In the dip-coating method, a fibrous sample is immersed in the coating solution for a certain time and then removed. Eventually, the adsorbed film is dried by the solvent evaporation. The coating thickness depends on the dipping time, the drying atmosphere, the solution viscosity, the withdrawal speed and the number of cycles [28].

The dip coating is also used to fabricate substrates for cell cultures. Immersing the cellulose mesh in a silk fibroin solution retains the three-dimensional microstructure of the cellulose substrate and contributes to its core-shell morphology (FIG. 2). The random secondary structure of silk fibroin present on the surface results in the better cell aggregation and formation of tumor spheroid [29].

Moreau et al. prepared a ligament implant of PVA fibers coated with PVA hydrogel and hydroxyapatite (HAp) via the combined dip-coating and physical cross-linking methods. The results indicated that the PVA/Hap layer did not significantly improve osseointegration as HAp was partially trapped within the PVA matrix, causing the inappropriate kinetics of its dissolution. However, the coating contributed to the reduction of fibrous tissue formation [30].

In our study of PCL fibrous scaffolds modified by the dip coating in the hyaluronic acid (HA) suspension, we obtained the non-uniform morphology of single fibers. The achieved layer was not homogeneous, but it did not lead to fiber sticking and the scaffolds did not lose their porosity. As a result, we observed a drop in the wettability of the fibrous scaffold (decrease of the wetting angle from 92° to 56°).

### Electrophoretic deposition

The EPD is a two-step process consisting of electrophoresis followed by deposition. In the first step, an external electric field causes the migration of colloidal charged molecules/particles towards the oppositely charged electrode. During the deposition, the stage particles accumulate and coagulate at the electrode surface. The deposition occurs either on the anode or cathode, depending on the surface charge of the molecule [31].

Thanks to the electrophoretic deposition, a surface with antifouling properties can be obtained. Thinakaran et al. deposited the chitosan and polyethylene glycol coating containing silver nanoparticles onto the surface of the fibrous PCL mat. As a result, they achieved a uniformly distributed layer containing an antimicrobial agent, which made the samples completely resistant to biofilm formation [32].

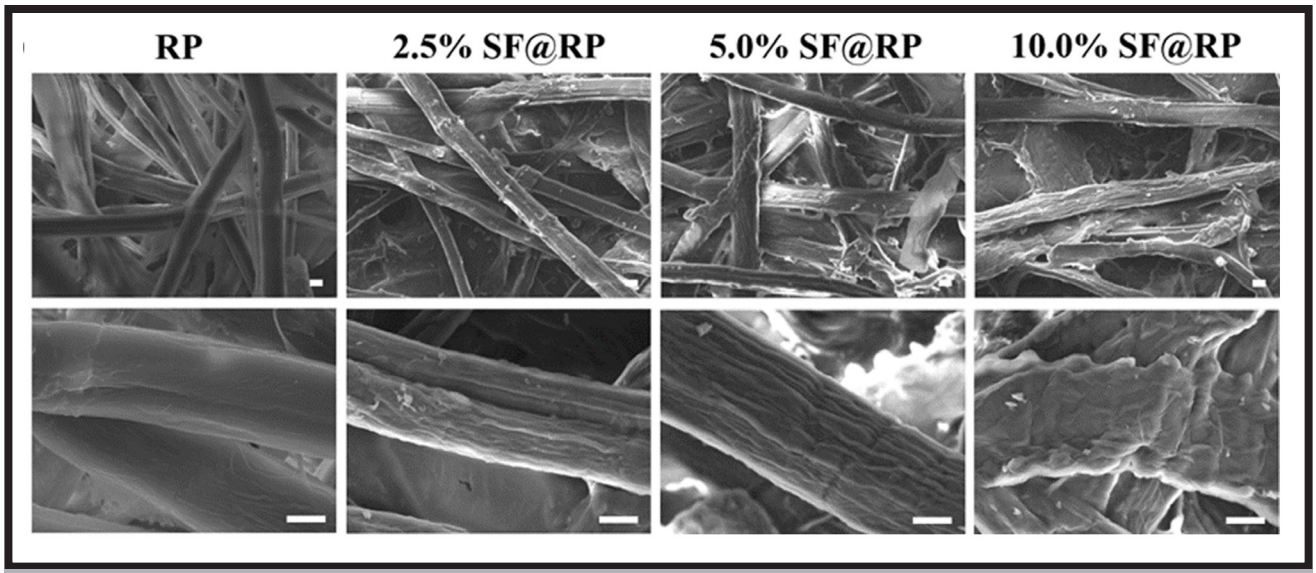


**FIG. 2. FESEM pictures of rice paper (RP) and SF@RP (silk fibroin@rice paper) at different concentrations of SF [29].**

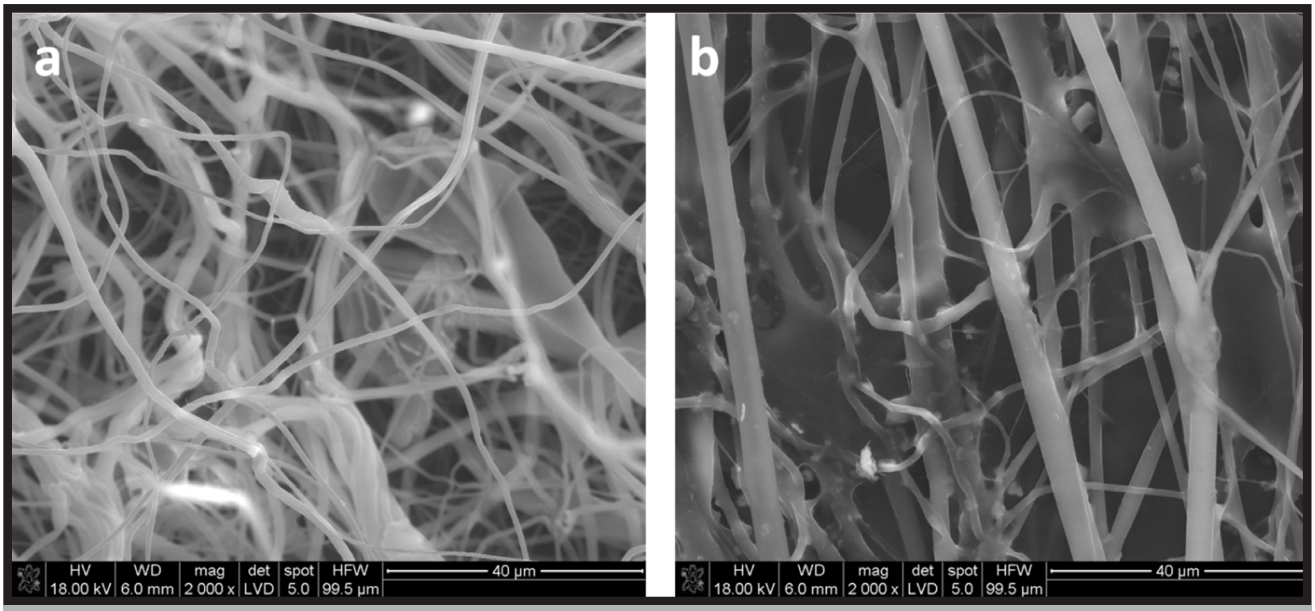


**FIG. 3. Unmodified cellulose acetate (CA) fibers (a) and CA fibers surface modified by EPD method in $SiO_2$ suspension (b) [35].**

In the case of porous materials, just as fibrous scaffolds, the main drawback of the EPD is the possibility of the pores blockage. Therefore, Taale et al. coated graphite fibers with hydroxyapatite nanoparticles using the periodic electrophoretic deposition. Their modification resulted in more uniformly covered fibers within the whole volume of the scaffold and the better promotion of osteoblasts activity [33].

This method could be also combined with other techniques of deposition. Yao et al. coated the graphene foam by a two-step process involving the dip coating in a poly(lactic-co-glycolic acid) and the electrodeposition of a chitosan and bone morphogenic proteins (BMP2) hybrid layer. The performed modifications improved mechanical properties and differentiated the human mesenchymal stem cells towards osteocytes caused by the BMP2 sustained release [34].

In the electrophoretic deposition method, the suspension composition must be carefully studied. Better results are observed if the suspension contains particles with the character (Dzeta potential) opposite to the chemical nature of the fiber material. If this condition is not fulfilled, agglomerates or solidified areas are observed on the fiber surface (FIG. 3).

**Electrospraying**

The electrospraying is a process in which a liquid is dispersed by a high electric field. As a result, nano- and submicron particles are formed [36]. The principles of electrospraying and electrospinning are similar. However, changing the solution properties (solvent, polymer concentration, viscosity) or process parameters (voltage, flow rate, distance between nozzle and collector) may lower the degree of the molecular interaction in the solution. Therefore, a droplet may form instead of a fiber [37,38]. Both methods could be also combined.

Jiajia Tang et al. produced a nanocomposite scaffold for nerve regeneration consisting of electrospun aligned PCL fibers. They modified its surface by electrospraying collagen and conductive polypyrrole nanoparticles (PPy NPs). The synergistic effect of the fiber orientation and conductive properties of electrosprayed PPy NPs provided appropriate mechanical properties and induced the neurite/axon elongation along the fibers. In combination with the external electrical stimulation, it also resulted in the enhanced neurogenesis [39].

In another study, Yuzhu He et al. prepared the nanocomposite chitosan (CS) and gelatin (Gln) guided bone regeneration membrane enriched in hydroxyapatite nanoparticles (nHAp) and antimicrobial peptides (AMP) (FIG. 4). Via the layer-by-layer electrospinning and electrospraying the osteogenic layer (CS/Gln/nHAp), the barrier layer (CS/Gln) and AMP-loaded PLGA microspheres embedded in between were formed. The results showed the excellent biocompatibility, osteogenic behaviour and long-term release of an antimicrobial agent, i.e. one week of bactericidal activity and antibacterial activity over one month (research conducted toward *E. coli* and *S. aureus*) [40]. Due to the particles morphology which ensures the adjustable release kinetics, the electrospraying is also widely used in the drug encapsulation [41].

**Co-electrospinning**

The first physical method used at the phase of the fiber mesh production is coelectrospinning. This surface modification has the same benefits as the traditional electrospinning, i.e. simplicity, possibility of using various materials and cost-effectiveness. Moreover, the addition of the second material with the different properties diminishes the drawbacks of the first one and thus improves the integration with the surrounding tissue [2,3].

Taskin et al. created a 3D scaffold consisting of PCL and polydopamine (pDA) by the single-step wet electrospinning. The hydrophilic pDA addition boosted the biocompatibility and the human mesenchymal stem cells adhesion as well as their penetration within the scaffold and differentiation towards fibroblasts [42]. Other biomolecules that could be incorporated into the scaffold are extracellular matrix components. Bhowmick et al. prepared co-electrospun nanofibers made of gelatin, chondroitin sulfate and sulfated hyaluronan which was modified with glycosaminoglycans. They observed a significant increase in the adhesion and proliferation of the mesenchymal stem cells, keratinocytes and fibroblasts [43].

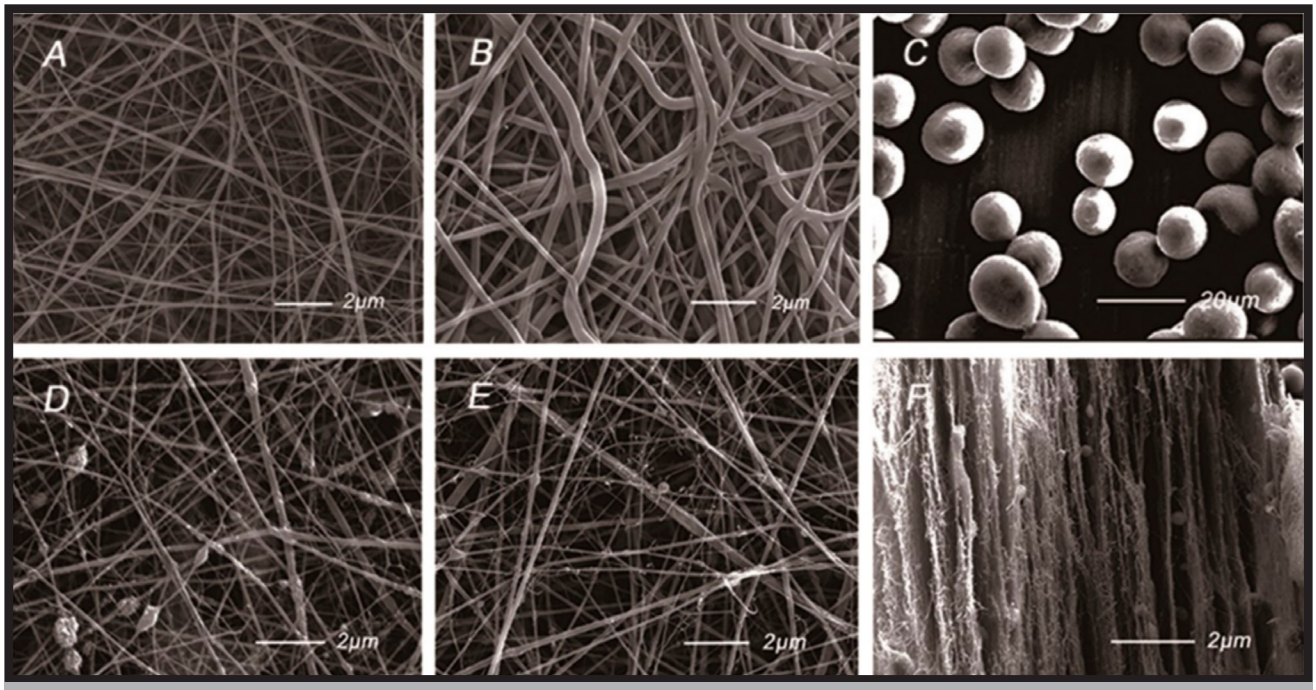


**FIG. 4. SEM images of the microstructure of the Gln/CS composite membrane before (A) and after (B) crosslinking; (C) Electrosprayed AMP@PLGA; The layer of Gln/CS/nHAp by magnetic stirring (D) and ultrasonic dispersion (E); (F) Cross-sectional image of the membrane [40].**

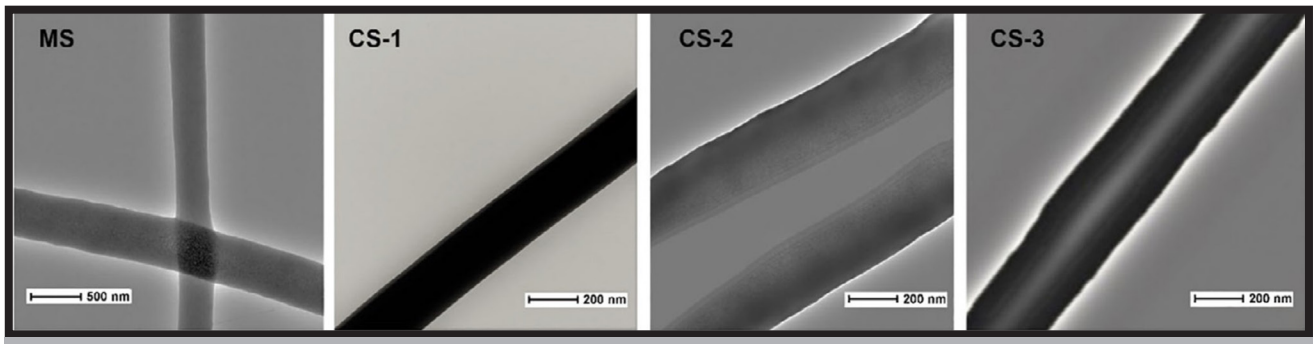


**FIG. 5. TEM images of monostructural and core-shell fibers [45].**

To improve the scaffold performance, the co-electrospinning can be combined with the surface grafting and used e.g. in bone tissue engineering. In the study conducted by Qingxia Zhu et al., the fibrous mesh consisting electrospun poly(ester urethane)urea (PEUU) was reinforced with $nTiO_2$. Moreover, poly(ester urethane) (PEU) was grafted onto the $nTiO_2$ to improve its interaction with the substrate. This approach resulted in the improved tensile strength (the increase of Young modulus) and better biomineralization and mesenchymal stem cells proliferation [44]. Another way of modification is the coaxial electrospinning. This approach has found a high interest in tissue engineering and wound healing applications (drug release). Eskitoros-Togay et al. used the coaxial electrospinning to produce fibers for the controlled release of doxycycline (DOXH). They prepared core/shell fibers of poly(ε-caprolactone)/poly(ethylene oxidase) loaded with DOXH in the core part (FIG. 5). The outcomes indicated that blending hydrophobic (PCL) and hydrophilic (PEO) polymers resulted in the more controlled drug release kinetics in the first 120 min, when compared to monolithic fibers [45].

**Layer by layer deposition**

The main advantages of this method are the possibility of producing multilayer coatings and the nanoscale control over deposited layers. In this technique, oppositely charged polymers are alternately deposited on the surface where they form an ultrathin and uniform film (FIG. 6). Moreover, the LBL uses natural forces, such as hydrogen bonding, electrostatic interactions and molecular interactions, which makes it cost-efficient [46]. The method has numerous benefits, such as: precise control over thickness and properties of the coating, homogeneity of the layers, versatility of the biomolecules and their controllable release [47]. Qian et al. used the layer by layer deposition to functionalize PCL nanofibers by silk fibroin. Additionally, heparin disaccharide (HD) was attached to the scaffold by the click chemistry to inhibit foreign body reaction and fibrosis development around it. The studies revealed that the HD incorporation resulted in the interleukin-4 (IL-4) adsorption which is responsible for the macrophages polarization toward M2 macrophages and, therefore, it improves anti-inflammatory properties of the PCL fibers [48].

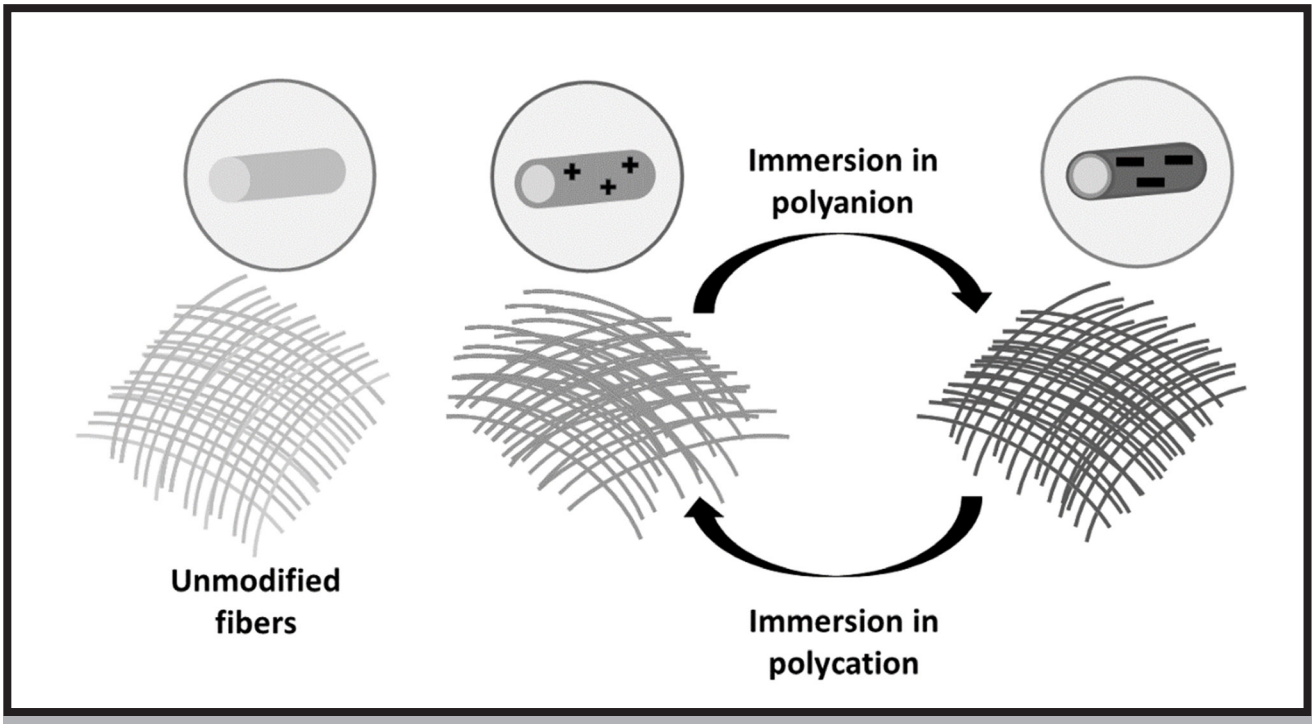


**FIG. 6. Schema of the LBL process.**

**Directional epitaxial crystallization**

Yet another way to modify the nanofiber surface is the directional epitaxial crystallization. Via this method the characteristic morphology called shish-kebab is formed (FIG. 7). It consists of the electrospun fiber which acts as a "shish" and of periodically arranged crystals which act as a "kebab". This type of morphology is achieved by immersing the scaffold in a crystal-forming polymer and the solution free chains crystallizing onto the surface of the electrospun fibers [49]. This method could be used with various materials, such as PLA [50], PCL [51] or PEO [52]. Guo et al. attempted to mimic ECM collagen fibrils by the self-induced crystallization on the PCL nanofibers. This modification enabled achieving the shish-kebab morphology which promoted further cell adhesion, migration and proliferation [51]. Such a method could be also used for bone regeneration. Liu et al. prepared a scaffold which consisted of co-electrospun PCL and β-tricalcium phosphate (β-TCP) which they modified by the self-induced crystallization. Both the presence of β-TCP and the shish-kebab morphology decreased the contact angle, protein adsorption and cellular adhesion. Moreover, the samples exhibited enhanced mechanical properties and biomineralization [53]. This method could be also combined with the coaxial electrospinning. Huang et al. prepared hierarchical core-shell nanofibers consisting of PCL as a shell and PVA as a core modified by the self-induced crystallization. Additionally, they enriched one group of the fibers with bone morphogenetic protein 2 (BMP2) in the core part. The results revealed that the shish-kebab morphology and the growth factor incorporation (BMP2) promoted the osteogenic cells differentiation. Moreover, a hierarchical structure of the scaffold allowed the sustained BMP2 release [54].

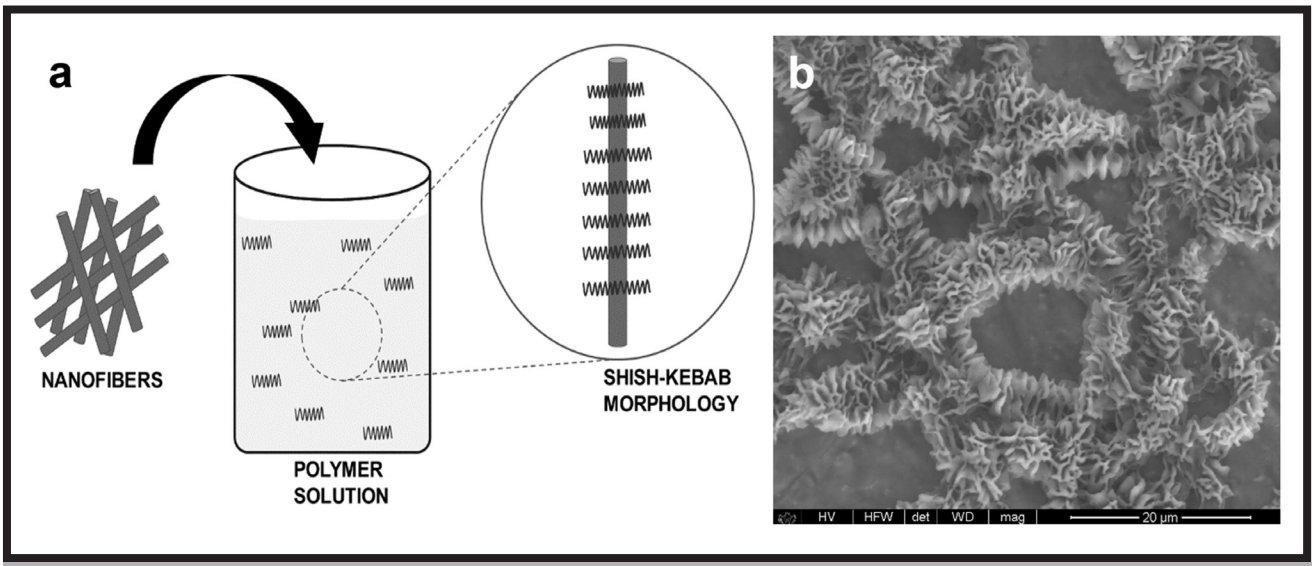


**FIG. 7. Schema of the directional epitaxial crystallization process (a) and SEM image of shish-kebab morphology (b) [55].**

## Chemical Surface Modification

Chemical modification techniques consist in forming covalent bonding between the surface and the immobilized agent. In comparison to the physical methods, the molecules attached to the surface via chemical modifications are less prone to being leached out. There are numerous approaches, such as the wet chemical modification, the plasma treatment, the surface grafting with peptides or copolymers [56].

**Chemical adsorption**

In the chemical adsorption method (also called chemisorption) the molecule on the substrate is immobilized when the electrons of the adsorbate and the adsorbent form a covalent or ionic bond. Therefore, the chemisorption requires a surface with a significantly higher free energy than in the physical adsorption [57]. If active functional groups are not present on the surface, its chemistry has to be modified [58]. One of the strategies is to activate the surface via the covalent immobilization by means of an intermediary linker, e.g. 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (EDC/NHS). In their research, Guler et al. used EDC/NHS to activate the COOH- groups of P3ANA immobilizing RGD peptide onto the surface of the poly(ε-caprolactone)/poly(m-anthranilic acid) (PCL/P3ANA) fibers. As a result, the better cell adhesion and osteogenic activity were observed [55]. Another approach involves adapter molecules. Biotin-avidin is stable, unaffected by the pH change or the subsequent washing complex coupled by a strong non-covalent bond [59]. Such a set of properties determines its use in biomedical applications, e.g. to immobilize growth factors on the surface of the fibrous scaffold for bone tissue regeneration. The activation of the gelatin nanofibers coated with HAp with avidin enabled the attachment of biotinylated growth factors (bone morphogenetic protein-2 (BMP-2) and fibroblast growth factor-2 (FGF-2)) to its surface. As a result, the release profile of the BMP-2 and FGF-2 was more efficient for the biotin-avidin complex than for the physical adsorption [60]. The chemisorption can also be used for capturing microspheres on the polymer fibers surface. Ahrens et al. activated the surface of fibrous poly(ethylene terephthalate) (PET) with carboxyl groups to immobilize biotin. Then, they examined the efficiency of capturing of the avidin-functionalized cells-containing microspheres under different flow variants. The biotin high affinity toward avidin led to the sufficient capturing of the microspheres under all the tested conditions (i.e. vigorous mixing and perfusion flow) [59].

**Surface grafting**

One of the most recent approaches in the surface modification is the peptide grafting. The obtained high bioactivity, stability and low immunogenicity of the material makes the peptide grafting a good alternative. The commonly used biomolecules include fibronectin, collagen, laminin and peptides originated from them as an attractor for endothelial cells, fibroblasts and keratinocytes [61-64]. Moreover, antibacterial properties could be obtained by the surface functionalization with antimicrobial peptides (AMP). The main advantage of the AMP over antibiotics is limiting the antibiotic resistance development [65]. The peptide grafting method also provides a signal to the host cells, which results in their better integration with the surrounding tissue. To improve the cell interaction this method can be also combined with growth factors. Studies by Emre Yüksel et al. proved that Magainin II and the epidermal growth factor attached to the PLGA fibers surface could result in both the increased cell proliferation and the reduced bacteria activity (S. aureus) [66]. One of the most commonly used peptides is RGD (arginine-glycine-aspartic acid) which originates from fibronectin. It regulates the endothelial cells adhesion, migration and proliferation. As RGD is recognized by different integrins, it acts as a nonspecific peptide. In their study, Ge Peng et al. used different types of peptides: fibronectin originated (RGD, REDV) and laminin originated (YIGSR) on the silk fibroin scaffolds to achieve the complex cellular response to improve the vascular graft endothelization. The modification increased the surface hydrophilicity and the cells adhesion. However, the platelet activation and the cell proliferation depended on the combination of peptides grafted on the surface, which means that the specific cell behaviour could be obtained by the peptides proper selection [64]. Another example is the immobilization of the RGDC signal peptide on the

γ-PGA fibers by the click chemistry. The scaffold can also be loaded with GS-Rg3 to heal wounds and inhibit scar formation. The results showed high biocompatibility of the samples as well as the better kinetics of the drug release [67].

**Wet-chemical modification**

In this method, reactive functional groups at the surface are generated by immersing the fiber mesh in liquid reagents. The process is usually carried out in an acidic or alkaline environment, which contributes to breaking the chain at the site of specific groups. Due to the wet chemical modification, functional groups including -OH, -COOH and $-NH_2$ appear at the surface [68].

One of the most common techniques is the aminolysis (FIG. 8) which introduces amino groups at the biomaterial surface and thus it serves as an intermediate step in the surface functionalization. S. Asadpour et al. used the aminolysis for further gelatin or collagen immobilization on the surface of vascular grafts made of poly(ether ester urethane) urea. The authors observed the improved cell adhesion and the endothelial cells layer formed on the implant [69]. Hoseinpour et al. prepared polyethersulfone (PES) membranes and modified them with carboxymethylcellulose (CMC) or sulphated carboxymethylcellulose (SCMC) which are extracellular matrix derived peptides. The membranes were immersed in the 10 wt% diethylenetriamine solution to introduce the $-NH_2$ groups on the surface. Then the samples were rinsed with ethanol for the aminolysis solution removal. The next step was the membranes incubation in a CMC or SCMC solution. The employed modifications lowered the contact angle, protein adsorption and platelet adhesion values, thus increasing the hemocompatibility. Moreover, the antifouling properties of the PES-CMC or PES-SCMC membranes were improved [70]. Another biomolecule which was grafted on the PLA fibrous scaffold by the aminolysis functionalization is an epidermal growth factor. The results showed the enhanced cell viability and proliferation [71].

The hydrolysis (FIG. 8) is another wet technique which incorporates -COOH group at the surface via the base or acid treatment. Thanks to the hydrolysis, the surface hydrophilicity and roughness could be increased [68]. Brown et al. used this method to improve the viability of human hepatocytes. In their study, a PLGA scaffold was prepared by the wet electrospinning. The mesh was immersed in the NaOH solution and then incubated in a solution of collagen I and fibronectin. Thanks to this modification, the microenvironment conducive to the hepatocytes survival was obtained. It ensured the higher albumin secretion and activity of the hepatocyte-specific gene in comparison to the reference samples [72].

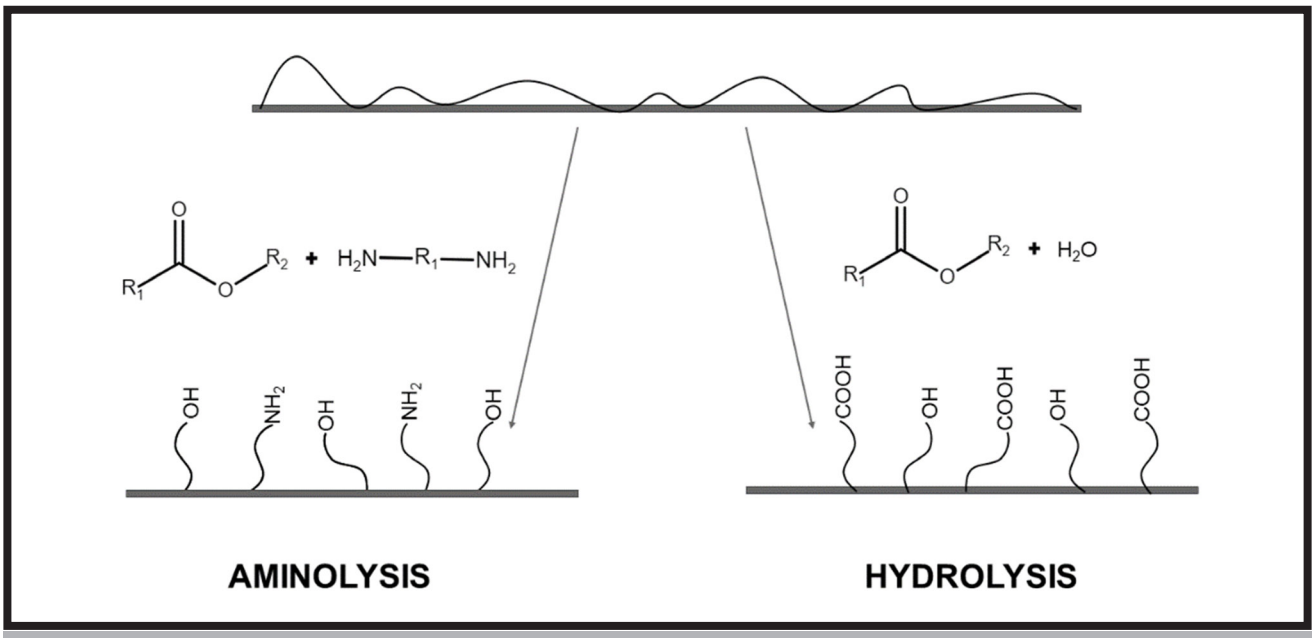


**FIG. 8. Surface chemistry after hydrolysis and aminolysis.**

It is also reported that combining the wet chemistry methods with adhesive molecules leads to the better cell-scaffold interaction. Pilipchuk et al. examined the impact of the different modifications on the PCL films biocompatibility. The applied methods were the amination, the hydrolysis, the fibronectin immobilization and the combination of hydrolysis with fibronectin incorporation. The results showed that, among all the options, the last approach had the best cellular response [73].

**Plasma treatment**

Another promising technique is the non-thermal plasma treatment of the fibers which enables the introduction of the various functional groups. This technique changes the surface properties without affecting its morphology. However, the outcomes are strongly dependent on two factors: the gas used for plasma creation and the time of the process. The samples treated with the argon plasma for a maximum time of 15s showed the unaltered fiber morphology, while those treated with the air plasma displayed the locally melted spots. Nevertheless, both methods increased the surface hydrophilicity by incorporating oxygen-containing groups [7].

Not only the oxygen-containing groups could be incorporated into the surface. In the research conducted by Mahtab Asadian et al., chitosan/polyethylene oxide nanofibrous mats were modified by the dielectric barrier discharge in the argon, nitrogen and ammonia/helium medium. Via the applied modification, polar functional groups (oxygen-containing and nitrogen-containing) were incorporated at the surface. The associated increase in free energy facilitated the cell adhesion. Another advantage was the increased tensile strength of the fibers [1]. In the next research, Mahtab Asadian et al. examined the plasma treatment effect before and after the electrospinning. The results indicated that the fibers morphology and surface chemistry were different when the plasma was applied before or after the process. In the first case, they achieved the beadless mesh with the unaltered surface properties. In the latter case, the surface wettability, as well as the cell adhesion and proliferation, increased without any changes in the fibers morphology [74]. There are many other studies on the plasma treatment used for the surface modification proving t its positive impact on the cells adhesion and mechanical properties [75-77]. The plasma pretreatment is also used to prepare surfaces for the physical deposition to enhance the coating adhesion. Akhavana et al. used the ion-assisted plasma pretreatment on the titanium surface. Then the material was immersed in the solution containing the antimicrobial peptides. Due to such a procedure, a covalent bond between the surface and molecules was formed [78].

**Mussel-inspired coating**

This biomimetic strategy is inspired by the adhesion mechanism governed by the mussel foot protein consisting of lysine and dihydroxyphenylalanine (DOPA). The catechol group in the lysine DOPA and amino groups interacts with the surface through electrostatic interactions, hydrogen bonds and covalent reactions. Dopamine is another molecule with both catechol and amino groups which can also self-polymerize on various substrates [79]. Carmagnola et al. used DOPA for the gelatin grafting on the surface of the PLGA electrospun membranes. This surface functionalization did not deteriorate the bulk material properties. The increased hydrophilicity improved the cellular adhesion and viability [80]. Chen et al. immobilized bromelain on the PCL electrospun membrane used for wound healing. Polydopamine (PDA) was applied as a linking agent between bromelain and the substrate. The BrPDA-PCL fibers exhibited good mechanical stability, very high hydrophilicity, biocompatibility and antibacterial behaviour against *E. coli* and *S. aureus*. The increased wound healing rate was observed during the *in vivo* examination [81].

Norepinephrine is another catecholamine molecule which could be used in tissue engineering. Liu et al. prepared a PCL fibrous scaffold coated with poly norepinephrine (pNE) via self-polymerization. The *in vitro* research revealed that the pNE addition facilitated the hydrophilicity and thus improved the skeletal muscle cell adhesion and proliferation. On the other hand, no toxic behaviour was observed during the 40-day *in vivo* examination [82]. The main drawback of this method is that it requires the alkaline environment for the dopamine polymerization and thus it cannot be used for materials that are unstable in these conditions. Another disadvantage is that this is a time-consuming process (up to several hours) [79].

## Conclusions

In this mini-review, the most recent methods of modifying electrospun fibers for tissue engineering were discussed. The main limitations of pristine electrospun scaffolds can be overcome thanks to the properly selected modification technique. The specific biomolecules immobilization leads to obtaining the desired and customized implant functionality, which results in its better integration with the surrounding tissues, mechanical support and bioactivity.

The fibers physical modifications have numerous advantages, such as simplicity, short time, and low cost. Unfortunately, the physical modifications are not durable and are only suitable where the material can be applied immediately after the process.

The chemical methods are more demanding and consist of many stages. Very often they require additional processing, e.g. preparing the fiber surface or selecting fiber materials that enable the formation of primary bonds. Moreover, the chemical modification is not always sufficiently effective due to the substrate form i.e. the fiber submicron and micrometer diameters. Instead of obtaining the homogeneous fiber surface, most often its domain character occurs. Chemical modifications are not durable either due to the low process efficiency, but often the post-treatment is accompanied by the second-order interactions which are more numerous and contribute to the increased durability of the new layer on the fiber. Such hybrid substrates seem to be the future of ECM scaffolds. At the moment, most works focus on material modifications via the peptide grafting because of the obtained high bioactivity and possibility to control the cellular response. Nevertheless, the long-term impact of this approach on the *in vivo* effectiveness and biocompatibility is still unknown. Since fibrous scaffolds are intended to be used inside the human body, the selection of an appropriate sterilization process should be taken under consideration. Electrospun fibers could be sterilized by any of the commonly used sterilization methods such as autoclave, dry heat, gamma radiation, ethylene oxide, plasma or ozone. However, the selection of an appropriate method is dependent upon material and its properties (e.g. structure, melting temperature, glass transition temperature), microstructure (fibers diameter, porosity) or presence of active molecules on the surface. It is also important to choose a sterilization method that does not change not only the morphology of the fibers but also their physicochemical properties and biological activity. In the case of gamma radiation, the possibility of changes in molecular structure due to chain scission should be also taken under consideration [83]. On the other hand UV sterilization could attenuate the release kinetics of the growth factors [84]. Therefore, there is still a big urge to know the impact of different methods of sterilization on the bioactivity of the modified fibrous scaffolds. Therefore, the full understanding of the implant-tissue interface and its influence on the human body are crucial to yet develop the most beneficial scaffolds for tissue engineering.

## Acknowledgements

*We thank Barbara Trybalska and Agnieszka Wojteczko for taking a number of SEM photos. This work was supported from the subsidy of the Ministry of Education and Science for the AGH University of Science and Technology in Kraków (Project No 16.16.160.557).*

### ORCID iDs

R. Kurpanik: https://orcid.org/0000-0002-7943-7509
E. Stodolak-Zych: https://orcid.org/0000-0002-8935-4811

## References

[1] M. Asadian, I. Onyshchenko, M. Thukkaram, P.S. Esbah Tabaei, J. Van Guyse, P. Cools, H. Declercq, R. Hoogenboom, R. Morent, N. De Geyter: Effects of a dielectric barrier discharge (DBD) treatment on chitosan/polyethylene oxide nanofibers and their cellular interactions. Carbohydr. Polym. 201 (2018) 402–415.
[2] Y. Ding, M. Floren, W. Tan: High-Throughput Screening of Vascular Endothelium-Destructive or Protective Microenvironments: Cooperative Actions of Extracellular Matrix Composition, Stiffness, and Structure, Adv. Healthc. Mater. 6 (2017).
[3] Q. Li, B. Zhang, N. Kasoju, J. Ma, A. Yang, Z. Cui, H. Wang, H. Ye: Differential and interactive effects of substrate topography and chemistry on human mesenchymal stem cell gene expression. Int. J. Mol. Sci. 19 (2018).
[4] Z. Guo, M. Ma, X. Huang, H. Li, C. Zhou: Effect of fiber diameter on proliferation and differentiation of MC3T3-E1 pre-osteoblasts. J. Biomater. Tissue Eng. 7 (2017) 162–169.
[5] L. Krishna, S. Nilawar, M. Ponnalagu, M. Subramani, C. Jayadev, R. Shetty, K. Chatterjee, D. Das: Fiber Diameter Differentially Regulates Function of Retinal Pigment and Corneal Epithelial Cells on Nanofibrous Tissue Scaffolds, ACS Appl. Bio Mater. 3 (2020) 823–837.
[6] F. Rezaei, T. Planckaert, C. Vercruysse, J. Verjans, P. Van Der Voort, H. Declercq, R. Hoogenboom, R. Morent, N. De Geyter: The Influence of Pre-Electrospinning Plasma Treatment on Physicochemical Characteristics of PLA Nanofibers, Macromol. Mater. Eng. 304 (2019) 1–16.
[7] R. Ghobeira, C. Philips, V. De Naeyer, H. Declercq, P. Cools, N. De Geyter, R. Cornelissen, R. Morent: Comparative study of the surface properties and cytocompatibility of plasma-treated poly-ε-caprolactone nanofibers subjected to different sterilization methods, J. Biomed. Nanotechnol. 13 (2017) 699–716.
[8] Z. Sarwar, E. Krugly, P.P. Danilovas, D. Ciuzas, V. Kauneliene, D. Martuzevicius: Fabrication and characterization of PEBA fibers by melt and solution electrospinning. J. Mater. Res. Technol. 8 (2019) 6074–6085.
[9] Y. Kara, K. Molnár: Revealing of process–structure–property relationships of fine polypropylene fiber mats generated via melt blowing. Polym. Adv. Technol. (2021) 1–17.
[10] T.L. Jenkins, S. Meehan, B. Pourdeyhimi, D. Little: Meltblown Polymer Fabrics as Candidate Scaffolds for Rotator Cuff Tendon Tissue Engineering, Tissue Eng. - Part A 23 (2017) 958–967.
[11] M. Castilho, D. Feyen, M. Flandes-Iparraguirre, G. Hochleitner, J. Groll, P.A.F. Doevendans, T. Vermonden, K. Ito, J.P.G. Sluijter, J. Malda: Melt Electrospinning Writing of Poly-Hydroxymethylglycolide-co-ε-Caprolactone-Based Scaffolds for Cardiac Tissue Engineering. Adv. Healthc. Mater. 6 (2017) 1–9.
[12] M. Gwiazda, S. Kumar, W. Świeszkowski, S. Ivanovski, C. Vaquette: The effect of melt electrospun writing fiber orientation onto cellular organization and mechanical properties for application in Anterior Cruciate Ligament tissue engineering. J. Mech. Behav. Biomed. Mater. 104 (2020).
[13] F.L. He, X. Deng, Y.Q. Zhou, T. Di Zhang, Y.L. Liu, Y.J. Ye, D.C. Yin: Controlled release of antibiotics from poly-ε-caprolactone/polyethylene glycol wound dressing fabricated by direct-writing melt electrospinning. Polym. Adv. Technol. 30 (2019) 425–434.
[14] M. Rafiei, E. Jooybar, M.J. Abdekhodaie, M. Alvi: Construction of 3D fibrous PCL scaffolds by coaxial electrospinning for protein delivery. Mater. Sci. Eng. C 113 (2020).
[15] M.M. Machado-Paula, M.A.F. Corat, M. Lancellotti, G. Mi, F.R. Marciano, M.L. Vega, A.A. Hidalgo, T.J. Webster, A.O. Lobo: A comparison between electrospinning and rotary-jet spinning to produce PCL fibers with low bacteria colonization. Mater. Sci. Eng. C 111 (2020).

[16] H. Luo, D. Gan, M. Gama, J. Tu, F. Yao, Q. Zhang, H. Ao, Z. Yang, J. Li, Y. Wan: Interpenetrated nano- and submicro-fibrous biomimetic scaffolds towards enhanced mechanical and biological performances. Mater. Sci. Eng. C 108 (2020) 110416.
[17] X. Wang, B. Ding, B. Li: Biomimetic electrospun nanofibrous structures for tissue engineering. Mater. Today 16 (2013).
[18] Y. Xu, G. Shi, J. Tang, R. Cheng, X. Shen, Y. Gu, L. Wu, K. Xi, Y. Zhao, W. Cui, L. Chen: ECM-inspired micro/nanofibers for modulating cell function and tissue generation. Sci. Adv. 6 (2020) 1–18.
[19] J. Ye, J. Si, Z. Cui, Q. Wang, K. Peng, W. Chen, X. Peng, S.C. Chen: Surface Modification of Electrospun TPU Nanofiber Scaffold with CNF Particles by Ultrasound-Assisted Technique for Tissue Engineering. Macromol. Mater. Eng. 302 (2017) 1–9.
[20] I. Carmagnola, E. Ranzato, V. Chiono: Scaffold functionalization to support a tissue biocompatibility, in: Funct. 3D Tissue Eng. Scaffolds Mater. Technol. Appl., Elsevier (2018) 255–277.
[21] F.J. O'Brien: Biomaterials & scaffolds for tissue engineering. Mater. Today 14 (2011) 88–95.
[22] X. Ren, Y. Feng, J. Guo, H. Wang, Q. Li, J. Yang, X. Hao, J. Lv, N. Ma, W. Li: Surface modification and endothelialization of biomaterials as potential scaffolds for vascular tissue engineering applications. Chem. Soc. Rev. 44 (2015) 5680–5742.
[23] N.R. Mohamad, N.H.C. Marzuki, N.A. Buang, F. Huyop, R.A. Wahab: An overview of technologies for immobilization of enzymes and surface analysis techniques for immobilized enzymes, Biotechnol. Biotechnol. Equip. 29 (2015) 205–220.
[24] J. Zhou, X. Guo, Q. Zheng, Y. Wu, F. Cui, B. Wu: Improving osteogenesis of three-dimensional porous scaffold based on mineralized recombinant human-like collagen via mussel-inspired polydopamine and effective immobilization of BMP-2-derived peptide. Colloids Surfaces B Biointerfaces 152 (2017) 124–132.
[25] D. Rana, K. Ramasamy, M. Leena, C. Jiménez, J. Campos, P. Ibarra, Z.S. Haidar, M. Ramalingam: Surface functionalization of nanobiomaterials for application in stem cell culture, tissue engineering, and regenerative medicine. Biotechnol. Prog. 32 (2016) 554–567.
[26] W.S. Chen, L.Y. Guo, C.C. Tang, C. Kang Tsai, H.H. Huang, T.Y. Chin, M.-L. Yang, Y.W. Chen-Yang: The Effect of Laminin Surface Modification of Electrospun Silica Nanofiber Substrate on Neuronal Tissue Engineering (2018).
[27] I. Jesswein, S. Uebele, A. Dieterich, S. Keller, T. Hirth, T. Schiestel: Influence of surface properties on the dip coating behavior of hollow fiber membranes, J. Appl. Polym. Sci. 135 (2018) 1–10.
[28] X. Wu, I. Wyman, G. Zhang, J. Lin, Z. Liu, Y. Wang, H. Hu: Preparation of superamphiphobic polymer-based coatings via spray- and dip-coating strategies, Prog. Org. Coatings 90 (2016) 463–471.
[29] J. Fu, X.B. Li, L.X. Wang, X.H. Lv, Z. Lu, F. Wang, Q. Xia, L. Yu, C.M. Li: One-Step Dip-Coating-Fabricated Core-Shell Silk Fibroin Rice Paper Fibrous Scaffolds for 3D Tumor Spheroid Formation, ACS Appl. Bio Mater. 3 (2020) 7462–7471.
[30] D. Moreau, A. Villain, M. Bachy, H. Proudhon, D.N. Ku, D. Hannouche, H. Petite, L. Corté: In vivo evaluation of the bone integration of coated poly(vinyl-alcohol) hydrogel fiber implants. J. Mater. Sci. Mater. Med. 28 (2017).
[31] M. Atiq Ur Rehman, Q. Chen, A. Braem, M.S.P. Shaffer, A.R. Boccaccini: Electrophoretic deposition of carbon nanotubes: recent progress and remaining challenges, Int. Mater. Rev. 0 (2020) 1–30.
[32] S. Thinakaran, A.M. Loordhuswamy, G.D. Venkateshwapuram Rengaswami: Electrophoretic deposition of chitosan/nano silver embedded micro sphere on centrifugal spun fibrous matrices – A facile biofilm resistant biocompatible material, Int. J. Biol. Macromol. 148 (2020) 68–78.
[33] M. Taale, D. Krüger, E. Ossei-Wusu, F. Schütt, M.A.U. Rehman, Y.K. Mishra, J. Marx, N. Stock, B. Fiedler, A.R. Boccaccini, R. Willumeit-Römer, R. Adelung, C. Selhuber-Unkel: Systematically Designed Periodic Electrophoretic Deposition for Decorating 3D Carbon-Based Scaffolds with Bioactive Nanoparticles, ACS Biomater. Sci. Eng. 5 (2019) 4393–4404.
[34] Q. Yao, J. Jing, Q. Zeng, T.L. Lu, Y. Liu, X. Zheng, Q. Chen: Bilayered BMP2 Eluting Coatings on Graphene Foam by Electrophoretic Deposition: Electroresponsive BMP2 Release and Enhancement of Osteogenic Differentiation, ACS Appl. Mater. Interfaces 9 (2017) 39962–39970.
[35] E. Stodolak-Zych, M. Gajek, A. Rapacz-Kmita, Ł. Zych, B. Kolesińska: Monitoring of the hydrolytic and enzymatic degradation process of fibrous polysaccharides-protein scaffolds, in: 13th Conf. Calorim. Therm. Anal. Polish Soc. Calorim. Therm. Anal., Zakopane, Poland (2018).
[36] S. Faraji, B. Sadri, B. Vajdi Hokmabad, N. Jadidoleslam, E. Esmaeilzadeh: Experimental study on the role of electrical conductivity in pulsating modes of electrospraying, Exp. Therm. Fluid Sci. 81 (2017) 327–335.
[37] R.M.D. Soares, N.M. Siqueira, M.P. Prabhakaram, S. Ramakrishna: Electrospinning and electrospray of bio-based and natural polymers for biomaterials development. Mater. Sci. Eng. C 92 (2018) 969–982.
[38] A. Alehosseini, B. Ghorani, M. Sarabi-Jamab, N. Tucker: Principles of electrospraying: A new approach in protection of bioactive compounds in foods. Crit. Rev. Food Sci. Nutr. 58 (2018) 2346–2363.
[39] J. Tang, C. Wu, S. Chen, Z. Qiao, P. Borovskikh, A. Shchegolkov, L. Chen, D. Wei, J. Sun, H. Fan: Combining Electrospinning and Electrospraying to Prepare a Biomimetic Neural Scaffold with Synergistic Cues of Topography and Electrotransduction, ACS Appl. Bio Mater. 3 (2020) 5148–5159.
[40] Y. He, Y. Jin, X. Wang, S. Yao, Y. Li, Q. Wu, G. Ma, F. Cui, H. Liu: An antimicrobial peptide-loaded gelatin/chitosan nanofibrous membrane fabricated by sequential layer-by-layer electrospinning and electrospraying techniques. Nanomaterials 8 (2018) 1–13.
[41] V.M. Giménez, N. Sperandeo, S. Faudone, S. Noriega, W. Manucha, D. Kassuha: Preparation and characterization of bosentan monohydrate/ε-polycaprolactone nanoparticles obtained by electrospraying. Biotechnol. Prog. 35 (2019) 1–11.
[42] M.B. Taskin, R. Xu, H. Gregersen, J.V. Nygaard, F. Besenbacher, M. Chen: Three-Dimensional Polydopamine Functionalized Coiled Microfibrous Scaffolds Enhance Human Mesenchymal Stem Cells Colonization and Mild Myofibroblastic Differentiation. ACS Appl. Mater. Interfaces 8 (2016) 15864–15873.
[43] S. Bhowmick, S. Rother, H. Zimmermann, P.S. Lee, S. Moeller, M. Schnabelrauch, V. Koul, R. Jordan, V. Hintze, D. Scharnweber: Biomimetic electrospun scaffolds from main extracellular matrix components for skin tissue engineering application – The role of chondroitin sulfate and sulfated hyaluronan, Mater. Sci. Eng. C 79 (2017) 15–22.
[44] Q. Zhu, X. Li, Z. Fan, Y. Xu, H. Niu, C. Li, Y. Dang, Z. Huang, Y. Wang, J. Guan: Biomimetic polyurethane/$TiO_2$ nanocomposite scaffolds capable of promoting biomineralization and mesenchymal stem cell proliferation (2018).
[45] M. Eskitoros-Togay, Y.E. Bulbul, N. Dilsiz: Controlled release of doxycycline within core/shell poly(ε-caprolactone)/poly(ethylene oxide) fibers via coaxial electrospinning. J. Appl. Polym. Sci. 137 (2020) 1–12.
[46] J. Lipton, G.M. Weng, J.A. Röhr, H. Wang, A.D. Taylor: Layer-by-Layer Assembly of Two-Dimensional Materials: Meticulous Control on the Nanoscale. Matter 2 (2020) 1148–1165.
[47] P. Gentile, I. Carmagnola, T. Nardo, V. Chiono: Layer-by-layer assembly for biomedical applications in the last decade. Nanotechnology 26 (2015) 422001.
[48] Y. Qian, L. Li, Y. Song, L. Dong, P. Chen, X. Li, K. Cai, O. Germershaus, L. Yang, Y. Fan: Surface modification of nanofibrous matrices via layer-by-layer functionalized silk assembly for mitigating the foreign body reaction. Biomaterials 164 (2018) 22–37.
[49] S.E. Gleeson, S. Kim, T. Yu, M. Marcolongo, C.Y. Li: Size-dependent soft epitaxial crystallization in the formation of blend nanofiber shish kebabs, Polymer (Guildf). 202 (2020) 122644.
[50] L. Yi, S. Luo, J. Shen, S. Guo, H.J. Sue: Bioinspired Polylactide Based on the Multilayer Assembly of Shish-Kebab Structure: A Strategy for Achieving Balanced Performances. ACS Sustain. Chem. Eng. 5 (2017) 3063–3073.
[51] X. Guo, X. Wang, X. Li, Y.C. Jiang, S. Han, L. Ma, H. Guo, Z. Wang, Q. Li: Endothelial Cell Migration on Poly(ε-caprolactone) Nanofibers Coated with a Nanohybrid Shish-Kebab Structure Mimicking Collagen Fibrils. Biomacromolecules 21 (2020) 1202–1213.
[52] W. Bingbing, L. Bing, X. Jie, C.Y. Li: Hierarchically ordered polymer nanofibers via electrospinning and controlled polymer crystallization. Macromolecules 41 (2008) 9516–9521.

[53] L. Liu, T. Zhang, C. Li, G. Jiang, F. Wang, L. Wang: Regulating surface roughness of electrospun poly(ε-caprolactone)/β-tricalcium phosphate fibers for enhancing bone tissue regeneration. Eur. Polym. J. 143 (2021) 110201.
[54] C. Huang, G. Yang, S. Zhou, E. Luo, J. Pan, C. Bao, X. Liu: Controlled Delivery of Growth Factor by Hierarchical Nanostructured Core-Shell Nanofibers for the Efficient Repair of Critical-Sized Rat Calvarial Defect. ACS Biomater. Sci. Eng. 6 (2020) 5758–5770.
[55] E. Dzierzkowska, S. Krupnik, R. Kurpanik, E. Stodolak-Zych: Polymeric shish-kebab fibers mimicking corneal stroma membrane, in: UK-PL Bioinspired Mater. Conf. 23-24th Novemb. 2020, 88.
[56] D. de Cassan, A. Becker, B. Glasmacher, Y. Roger, A. Hoffmann, T.R. Gengenbach, C.D. Easton, R. Hänsch, H. Menzel: Blending chitosan-g-poly(caprolactone) with poly(caprolactone) by electrospinning to produce functional fiber mats for tissue engineering applications, J. Appl. Polym. Sci. 137 (2020) 1–11.
[57] S. Kwon, M. Fan, H.F.M. DaCosta, A.G. Russell, K.A. Berchtold, M.K. Dubey: $CO_2$ Sorption, in: Coal Gasif. Its Appl., Elsevier (2011) 293–339.
[58] M. Najafi, M.W. Frey: Electrospun nanofibers for chemical separation. Nanomaterials 10 (2020).
[59] L. Ahrens, D. Vonwil, N. Arya, A. Forget, V.P. Shastri: Biotin-avidin-mediated capture of microspheres on polymer fibers. Molecules 24 (2019) 1–15.
[60] N. Udomluck, H. Lee, S. Hong, S.H. Lee, H. Park: Surface functionalization of dual growth factor on hydroxyapatite-coated nanofibers for bone tissue engineering. Appl. Surf. Sci. 520 (2020) 146311.
[61] R. Daum, D. Visser, C. Wild, L. Kutuzova, M. Schneider, G. Lorenz, M. Weiss, S. Hinderer, U.A. Stock, M. Seifert, K. Schenke-Layland: Fibronectin Adsorption on Electrospun Synthetic Vascular Grafts Attracts Endothelial Progenitor Cells and Promotes Endothelialization in Dynamic In Vitro Culture. Cells 9 (2020) 778.
[62] A. Ravindran Girija, V. Palaninathan, X. Strudwick, S. Balasubramanian, S. Dasappan Nair, A.J. Cowin: Collagen-functionalized electrospun smooth and porous polymeric scaffolds for the development of human skin-equivalent. RSC Adv. 10 (2020) 26594–26603.
[63] G. Li, K. Chen, D. You, M. Xia, W. Li, S. Fan, R. Chai, Y. Zhang, H. Li, S. Sun: Laminin-Coated Electrospun Regenerated Silk Fibroin Mats Promote Neural Progenitor Cell Proliferation, Differentiation, and Survival in vitro. Front. Bioeng. Biotechnol. 7 (2019) 190.
[64] G. Peng, D. Yao, Y. Niu, H. Liu, Y. Fan: Surface Modification of Multiple Bioactive Peptides to Improve Endothelialization of Vascular Grafts. Macromol. Biosci. 19 (2019) 1–12.
[65] H.P. Felgueiras, M.T.P. Amorim: Functionalization of electrospun polymeric wound dressings with antimicrobial peptides. Colloids Surfaces B Biointerfaces 156 (2017) 133–148.
[66] E. Yüksel, A. Karakeçili, T.T. Demirtaş, M. Gümüşderelioğlu: Preparation of bioactive and antimicrobial PLGA membranes by magainin II/EGF functionalization. Int. J. Biol. Macromol. 86 (2016) 162–168.
[67] T. Xu, R. Yang, X. Ma, W. Chen, S. Liu, X. Liu, X. Cai, H. Xu, B. Chi: Bionic Poly(γ-Glutamic Acid) Electrospun Fibrous Scaffolds for Preventing Hypertrophic Scars. Adv. Healthc. Mater. 8 (2019) 1–12.
[68] B. Niemczyk-Soczynska, A. Gradys, P. Sajkiewicz: Hydrophilic surface functionalization of electrospun nanofibrous scaffolds in tissue engineering. Polymers (Basel). 12 (2020) 1–20.
[69] S. Asadpour, H. Yeganeh, J. Ai, H. Ghanbari: A novel polyurethane modified with biomacromolecules for small-diameter vascular graft applications. J. Mater. Sci. 53 (2018) 9913–9927.
[70] V. Hoseinpour, A. Ghaee, V. Vatanpour, N. Ghaemi: Surface modification of PES membrane via aminolysis and immobilization of carboxymethylcellulose and sulphated carboxymethylcellulose for hemodialysis. Carbohydr. Polym. 188 (2018) 37–47.
[71] T. Haddad, S. Noel, B. Liberelle, R. El Ayoubi, A. Ajji, G. De Crescenzo: Fabrication and surface modification of poly lactic acid (PLA) scaffolds with epidermal growth factor for neural tissue engineering. Biomatter 6 (2016) e1231276.
[72] J.H. Brown, P. Das, M.D. DiVito, D. Ivancic, L.P. Tan, J.A. Wertheim: Nanofibrous PLGA electrospun scaffolds modified with type I collagen influence hepatocyte function and support viability in vitro. Acta Biomater. 73 (2018) 217–227.
[73] S.P. Pilipchuk, A. Monje, Y. Jiao, J. Hao, L. Kruger, C.L. Flanagan, S.J. Hollister, W. V. Giannobile: Integration of 3D Printed and Micropatterned Polycaprolactone Scaffolds for Guidance of Oriented Collagenous Tissue Formation In Vivo, Adv. Healthc. Mater. 5 (2016) 676–687.
[74] M. Asadian, S. Grande, I. Onyshchenko, R. Morent, H. Declercq, N. De Geyter: A comparative study on pre- and post-production plasma treatments of PCL films and nanofibers for improved cell-material interactions, Appl. Surf. Sci. 481 (2019) 1554–1565.
[75] S. Surucu, K. Masur, H. Turkoglu Sasmazel, T. Von Woedtke, K.D. Weltmann: Atmospheric plasma surface modifications of electrospun PCL/chitosan/PCL hybrid scaffolds by nozzle type plasma jets for usage of cell cultivation. Appl. Surf. Sci. 385 (2016) 400–409.
[76] N. Ojah, D. Saikia, D. Gogoi, P. Baishya, G.A. Ahmed, A. Ramteke, A.J. Choudhury: Surface modification of core-shell silk/PVA nanofibers by oxygen dielectric barrier discharge plasma: Studies of physico-chemical properties and drug release behavior. Appl. Surf. Sci. 475 (2019) 219–229.
[77] N. Ojah, R. Borah, G.A. Ahmed, M. Mandal, A.J. Choudhury: Surface modification of electrospun silk/AMOX/PVA nanofibers by dielectric barrier discharge plasma: physiochemical properties, drug delivery and in-vitro biocompatibility. Prog. Biomater. 9 (2020) 219–237.
[78] B. Akhavan, T.D. Michl, C. Giles, K. Ho, L. Martin, O. Sharifahmadian, S.G. Wise, B.R. Coad, N. Kumar, H.J. Griesser, M.M. Bilek: Plasma activated coatings with dual action against fungi and bacteria. Appl. Mater. Today 12 (2018) 72–84.
[79] Z. Wang, H.C. Yang, F. He, S. Peng, Y. Li, L. Shao, S.B. Darling: Mussel-Inspired Surface Engineering for Water-Remediation Materials. Matter 1 (2019) 115–155.
[80] I. Carmagnola, V. Chiono, G. Ruocco, A. Scalzone, P. Gentile, P. Taddei, G. Ciardelli: PLGA membranes functionalized with gelatin through biomimetic mussel-inspired strategy. Nanomaterials 10 (2020) 1–17.
[81] X. Chen, X. Wang, S. Wang, X. Zhang, J. Yu, C. Wang: Mussel-inspired polydopamine-assisted bromelain immobilization onto electrospun fibrous membrane for potential application as wound dressing. Mater. Sci. Eng. C 110 (2020) 110624.
[82] Y. Liu, G. Zhou, Z. Liu, M. Guo, X. Jiang, M.B. Taskin, Z. Zhang, J. Liu, J. Tang, R. Bai, F. Besenbacher, M. Chen, C. Chen: Mussel Inspired Polynorepinephrine Functionalized Electrospun Polycaprolactone Microfibers for Muscle Regeneration. Sci. Rep. 7 (2017) 1–10.
[83] C.F. Rediguieri, R.C. Sassonia, K. Dua, I.S. Kikuchi, T. de Jesus Andreoli Pinto: Impact of sterilization methods on electrospun scaffolds for tissue engineering. Eur. Polym. J. 82 (2016) 181–195.
[84] O. Evrova, D. Kellenberger, C. Scalera, M. Calcagni, P. Giovanoli, V. Vogel, J. Buschmann: Impact of UV sterilization and short term storage on the in vitro release kinetics and bioactivity of biomolecules from electrospun scaffolds. Sci. Reports 2019 91, 9 (2019) 1–11.