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# A Brief Review on Prospective of Polyvinylidene Fluoride as a Tissue Engineered Scaffold Material

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**Abstract:** This review focuses on the potential of polyvinylidene fluoride (PVDF) as tissue scaffolding materials. PVDF is defined in terms of the synthesis mechanisms and the method of the β phase formation process. General properties are fundamentally discussed in terms of their wettability and electroactive characteristics, which play an essential role in modifying other potential materials for tissue-based applications. The latest technologies for the replacement of artificial tissue scaffolds are evaluated, and the applications of PVDF-based scaffolds are discussed.

**Keywords:** Tissue engineering, Polyvinylidene fluoride, Electroactive polymer, Electrospinning, 3D printing

## 1. Introduction

Human organs can maintain their homeostasis, circulating blood, and adapting accordingly as a response to several changes from their surroundings. The loss of functionality, however, is, in fact, inevitable, mainly due to aging or disease/injury. Nonetheless, injured tissues and even entire organs have the potential of regeneration, supported by conventional medical therapy, transplantation, and new experimental approaches that emerged from the exciting area of regenerative sciences [1-2]. Regenerative sciences are an interdisciplinary field that utilizes engineering and life science concepts to facilitate the regeneration process. Theoretically, it can regenerate or restore diseased and damaged tissues along with entire organs. Tissue engineering is a field that develops tools for solving problems in regenerative sciences by manufacturing an artificial tissue scaffold. The result of tissue engineering can generally be known as the merging of biological, chemical, and engineering principles that create and develop new biological substitutes that can help fix, replace, sustain, or enhance the tissue or whole organ [3]. Tissue engineering thus appears to be the best solution to close the gaps in the existing tissue defects in reconstructive surgery. It may hamper various of the complications and problems associated with donor organs, albeit at a lower cost [4-5]. The importance of stem cells, tissue engineering, and advanced materials have been recognized in recent trends as a new strategic research direction for disciplines in biology and physical sciences, named "regenerative engineering" [6]. Regenerative engineering focuses on the regeneration or reconstruction of the involved tissue and biological systems. Nonetheless, tissue engineering only aims specifically at the ability to repair specific tissue.

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Three components needed in tissue engineering before injured or diseased tissues and organs can be replaced or rebuilt are (1) cells harvested from the donor tissue such as nerve, pancreas, skin, liver, bone cells, and stem cells; (2) supporting biomaterial scaffolds, aiding in cell attachment, proliferation and development; and (3) biomolecules, such as growth factors and cytokines. The scaffolds have a significant role in tissue engineering strategies. It must have an architectural framework where the cells and the growth factors will interact to create a functionalized biological construct that meets regenerative medicine requirements. A promising scaffold must exhibit several critical requirements, such as biodegradable, biocompatible, excellent mechanical properties, highly porous, and malleable with a large surface/volume ratio [7]. After implantation, the scaffold will either be degraded after new organs or tissues are formed, while it will remain without adversely affecting current tissues or organs and developing them.

Ideal materials for the manufacture of scaffolds should induce desirable cellular interactions to aid in the formation of new functional tissues for medical use. The scaffolds must mimic the native tissue's ECM in order to enable cells to influence their surrounding microenvironments [8]. Scaffold materials must meet specific essential criteria to achieve tissue engineering goals. It needs a hydrophilic, high porosity, and sufficient pore size to allow the seeding and diffusion of both nutrients and cells across the entire structure. Besides, biodegradability is also essential as the underlying tissues can ideally absorb the scaffold without the need for surgical removal [9-10]. Until further research on cell seeding patterning and regeneration of new complex tissue, the selection of scaffolding materials is therefore crucial and significant task.

There are different types of material in the previous study that can be used to manufacture tissue scaffolds, especially the electrical conductive polymers includes poly (3,4-ethylene dioxythiophene) [11], polyaniline [12], polypyrrole (PPy) [13], multi-walled carbon nanotubes (MWCNTs) [14], and polyvinylidene fluoride (PVDF) [15] which show good conductivity and low cytotoxicity to enhance neuritis and axonal outgrowth of specific tissues. Among these materials, PVDF has received significant attention due to its unique properties. It has the piezoelectric, pyroelectric, and ferroelectric properties, which can enhance the growth of electroactive cells, including nerve, heart, muscle, and bone-like [16]. PVDF is a semi-crystalline polymer compound that can occur in various potential phases of polymorphism such as α, β, π, and π [17]. Previous research on PVDF electrospinning has demonstrated a dominant orientation of crystalline polar β-phase crystal structure along a fiber axis that gives high electrical conductivity behaviors that make it ideal for tissue engineering [18]. Hence, PVDF's piezoelectric properties can guide cells without involving an external power supply, allowing direct electrical stimulation delivery.

Henceforth this analysis will address the overview approach to tissue engineering applications for polyvinylidene fluoride (PVDF). To offer an overview of PVDF before it can be stated as a potential material in regenerative medicine applications, the basic structure, synthesis process, β phase formation, and general properties are discussed comprehensively. Thus, it can be used in tissue engineering, which is essential in the imitation and enhancement of the natural extracellular matrix (ECM).

## 2. Basic Structure and Synthesis Pathway of PVDF

Due to its special piezoelectric, pyroelectric and ferroelectric characteristics, PVDF is preferable for generating nanofibers. PVDF can be described as a unique chemically inert thermoplastic fluoropolymer synthesized with vinylidene fluoride polymerization. Moreover, PVDF also possessed several useful characteristics, which include lightweight, good flexibility, high purity, excellent solvent resistance, and high electric field stability. PVDF's unique piezoelectric properties can be applied for various advanced nanofibers applications such as energy harvesters, force sensors, and transducers. Its capability to generate a high amount of voltages with only minimum forces allows piezoelectricity to be very beneficial. PVDF's polar crystalline structure is the main explanation behind its superior piezoelectric efficiency. The molecular structure arrangement of PVDFis consists of repeated monomer units such as (-$CH_2$-$CF_2$-)n with a 50% crystallinity. The crystallites are trapped in an amorphous domain and a 177 $^oC$ low melting point [19-20].

Based on the chain conformation (order of polymer chains in unit cells) as trans or gauche links, depending on the types of processing method, PVDF displays five different types crystalline polymorphs (α. β, γ, δ, and ε phases), which depending on how the final product was made. The only polymorph displaying piezoelectric existence is the β phase with a heavy dipole moment. It has an oriented unit cell of hydrogen and fluoride and the carbon backbone, making it beneficial in the most nanofibers applications since it can act as hydrogen-bond receptors where it can sense or recognize other molecules give colossal benefit during the interaction with other materials, drugs, or cells. Nevertheless, its α phase is the most abundant type of PVDF available. Thus, by applying a high electric field and stretching, the nonpolar α phase can be transformed into the polar β phase [21-22].

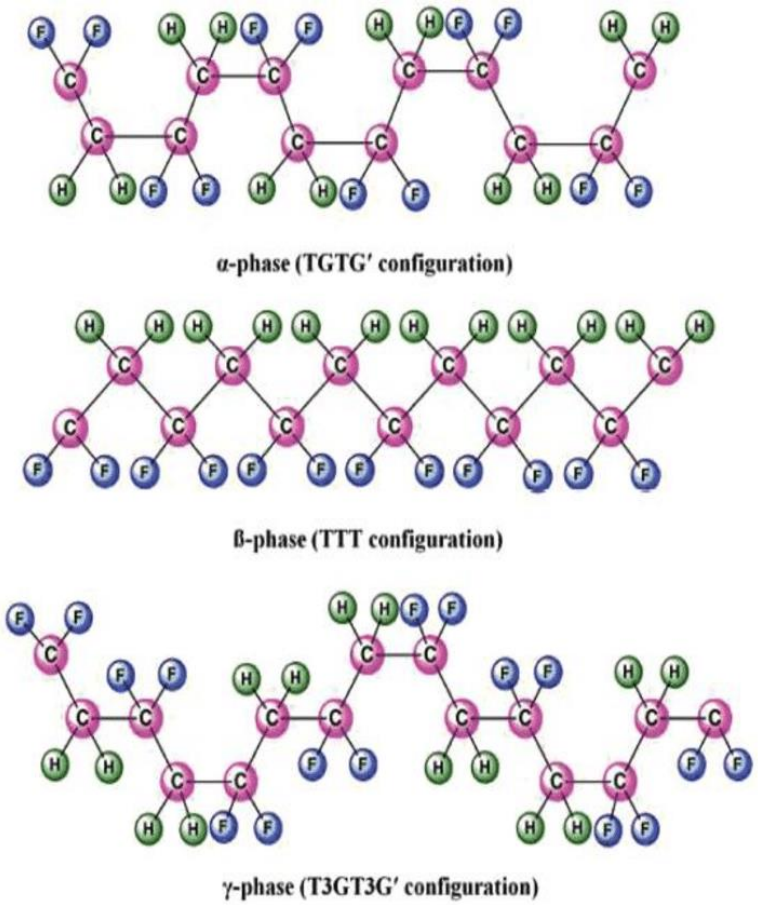


**Fig. 1 - α, β, and γ crystalline phases chain conformation diagrams [23]**

PVDF can typically be synthesized through 3 pathways by free radical polymerization processes, initiations distinct from radical ones, and finally by cobalt-mediated radical polymerization. The free radical or also known as controlled radical, occurred where PVDF developed as a heterogeneous reaction where it requires a fluorinated surfactant from a radical-induced batch polymerization process in the conditions of either aqueous emulsion or suspension (involving pressures in between of 10 to 300 atm) and temperatures of 10 to 130°C. Link or buffer transfer agents, or both can be used. Meanwhile, salts, disuccinic acid peroxide, sometimes hydroxyalkylperoxide, or alkylperoxybutyric acid can be used as water-soluble process initiators [24]. Organosoluble initiators involved in the second process are diisopropyl peroxy dicarbonate, tert-butyl peroxy pivalate, or tert-amylperoxypivalate, or ditert-butyl peroxide. In contrast, water-soluble polymers such as cellulose derivatives or poly (vinyl alcohol) (PVA) are used as suspenders to suppress polymer particle coalescence. Lastly, organic peroxides (such as bis (perfluoropropionyl) peroxide, bis-4-tert-butylperoxycyldicarbonate, or tert-butylperoxypivalate) in which the oxygen-oxygen bond initiate a homolytic scission with the presence of chlorofluorinated solvents were also investigated for solution polymerisation. Polymerized suspension and emulsion -VDF shows dissimilar behaviors in solution. Various solvents (DMF, NMP, DMSO, dimethylacetamide) are readily soluble in the suspension resin [24-25].

Then, for initiations other than the radical one pathway, the trialkyl aluminum and other low-temperature systems have proven to be effective "initiators" that generate minimum chaining defects (< 2.4%). Furthermore, the polymerisation of VDF initiated by oxygen-activated alkylboron compounds, pioneered by Natta in 1965, was later further investigated and studied by Chung's group. Interestingly, the device can regulate VDF polymerization that acts as a counter-radical [23,25]. For the controlled synthesis of PVDF, the organometallic-mediated radical polymerization (OMRP) of vinylidene fluoride (VDF) using an alkyl cobalt(III) compound as the initiator has recently proven successful [26]. The straightforward synthesis of well-defined poly(VDF) and its block copolymers through OMRP was performed from readily available compounds using a two-component initiating method. Next, redox initiation with the combination of a peroxide initiator and bis(acetylacetonato)cobalt(II) (C0(acac)2) was used to obtain PVDF. This step has been optimized in terms of the initiator's choice, the temperature of polymerization, and the molar reactant ratio. Use bis(tert-butylcyclohexyl) peroxydicarbonate act as an initiator at 60 °C, the best results were obtained for molar mass regulation and dispersities. Polymerization followed first-order kinetics, and PVDF molar masses increased linearly up to a conversion of 27% to reach 11 800 g / mol with low dispersion (Dj = 1.35). The subsequent chain extension of PVDF-Co(acac)2 with vinyl acetate (VAc) resulted in three diblock copolymers with varying chain lengths [26-27].

# 3. Formation of PVDF β Phase

## 3.1 Processing formation of β-Phase in PVDF Homopolymer

The large percentage content of β-phase PVDF with regard to its large piezoelectric, pyroelectric and ferroelectric applications is highly desired. Nevertheless, the non-polar of α-phase is more desirable formed when a PVDF homopolymer is crystallized out of the melt or solution. Although the polar β-phase possessed the most thermodynamically polymorphic for PVDF, it can only be obtained through the melting or crystallizing of the solution under certain conditions or by post-treatment of β-phase PVDF [24]. Doll and Lando were the first investigated and concluded that crystallization of PVDF melts caused by high pressure facilitated the formation of β-phase, the exclusive form when crystallized at 285 °C below 550 MPa [24,28]. A similar result showed that the crystallisation of PVDF melts at 260 °C through pressure quenching below 600 MPa yielded 100% β-phase PVDF [29]. With regard to the crystallization temperature, it has been reported that the samples displayed essentially the β-phase as the result of PVDF melt crystallized less than 30°C while quenching at the temperature above 70°C will result to the predomination of α-phase in the crystal structure [24]. Furthermore, the selection of the cooling rate above 150 $Ks^{-1}$ contributes to the formation of the β-phase, as shown by an additional low-temperature shoulder in the exothermic crystallisation. As the cooling rate is further increasing to 2000 $Ks^{-1}$, only the low exothermic peak was observed, which indicates the formation of pure β-phase [30-31].

PVDF crystallisation solution able to promote β-phase when selecting suitable solvents and processing conditions. Extremely polar solvents such as N, N-dimethyl formamide (DMF), dimethyl acetamide (DMAc), N-methyl-2-pyrrolidone (NMP), and hexamethylphosphoramide (HMPA) demonstrate strong inducing β-phase formation capabilities [32]. The temperature of crystallisation or the rate of evaporation (inverse to the temperature of the solution) plays a key role in deciding the fractions of crystal polymorphs. It was stated that crystallization from the PVDF / DMAc cast solution provided exclusively the β-phase at temperatures below 70 ° C, whereas the development of the α-phase began with beyond increasing temperature and predominated above 110 ° C [24-25]. Furthermore, a high fraction of β-phase can be obtained through the post-treatment process such as mechanical stretching where It has been reported that it much more effective and reliable than the in-situ crystallisation control strategy. The stress applied during the stretching process induce the rearrangement of the original α-phase with TGTG' chain conformation into the β crystal phase with all- transformation. The stretching parameters including the stretching temperature, stretching ratio, and strain rate directly affect the composition of the β phase [33]. It has been reported that by applying a stretching ratio of 5 at a temperature of 80 °C, a maximum value of β-phase of around 80% can be obtained, while further raising the stretching temperature will result to the decreases the efficiency of the α- to β-phase transformation. This is due to high temperatures that will enhance the chain mobility which will promote the crystal orientation along the stretching direction rather than a conformation change [24,34].

Additionally, by applying high external electric fields to α-phase PVDF will induce the formation of β-phase. The formation of the final β-form from the non-polar α-form will take place in 2 stages [35]. When polarized at room temperature under a moderate field (125 MVm−1), only a large fraction of the normal dipoles on the chain axis responded to the applied filed which directly result in the alignment of the neighboring molecular chains to crease stable polar π-phase with a minor alter in chain conformation. The α- to β- form crystal phase transition may be observed as the electric field is further increasing to 500 MVm−1 [36].

## 3.2 Electrospinning as a Promising Processing Technique

In recent decades, a few new processing technologies were developed and applied to the PVDF-based polymers to regulate the structure and improve material performance precisely. The electrospinning method has become a promising method for producing PVDF-based piezoelectric polymers, combining mechanical stretching with electric poling, since this technique can generate polar ß-phases and simultaneously harmonize dipoles during the process [37-38]. A standard spinning device consists of several parts, including a high voltage power supply, a syringe, and a screen collector for collecting the delicate fibers. During the electrospinning process, a polymer jet stream is ejected from the syringe needle at high voltage conditions and then landed on a grounded screen collector. Mechanical stretching and electrical poling coincide during the fiber solidification process. Moreover, polymer solution properties such as solvent polarity and solution concentration, greatly influence the fiber morphology, the crystalline structure of the fibers, and therefore on the ferroelectric and piezoelectric properties of the final product in electrospinning parameters, including the amount of voltage applied, tip-to-collector distance, and rotational speed [39]. By optimizing the electrospinning process parameters, a high fraction of a well-aligned β crystal stage and desirable piezoelectric properties can be obtained without an additional polling process distinctive of the strength spinning method in PVDF or PVDF-TrFE fibers. This piezoelectric PVDF and PVDF-TrFE fibers for biological and energy harvesting applications have been widely explored [24,40].

## 4. General Properties of PVDF

The most significant property of PVDF used to the greatest extent in the manufacture of nanofibers is its piezoelectric property. PVDF properties are very useful for piezoelectricity due to its potential to generate high voltages with minimum forces [19]. The piezoelectric effect can be defined as the phenomena of linear electromechanical interaction in crystalline material between the electrical and mechanical conditions. The effect is in nature reversible. In contrast, an internal electrical load able to be generated through the presence of mechanical stress while an applied external electric field to the material can develop an internal mechanical load. The Curie brothers first discovered piezoelectricity in 1880 [19,22]. One of the key parameters that determine a sample's piezoelectrical performance is its piezoelectric coefficient (D33). This measures the changes in the volume of the material that occurred when a piezoelectric material is put in an electric field or the ratio of polarization to the stress applied can be described. Typically, there are two types of piezoelectric coefficients which are the piezoelectric charging constant denoting the 'd' and piezoelectric tension constant denoting the 'g.' The piezoelectric charging coefficient gives polarization generated by mechanical stress per unit, and the electric field generated by the piezoelectric material by the mechanical stress unit is applied by the voltage coefficient. By knowing the value of D33, the material suitability for stress-related applications can be easily identified. The coefficient is generally called Dxy and its number is based on the direction of polarization and the direction of stress [19-21,41].

As PVDF possessed a high potential piezoelectric effect reported, the ferroelectric property of PVDF was anticipated. The hysteresis loop was successfully observed in 1974 [22]. PVDF has great potential to be used as organic ferroelectric material in multifunctional MR devices. The presence of the dipole moments in the PVDF molecular structure results in PVDF possessed a ferroelectric effect. The dipole moments are due to the presence of highly electronegative charged fluoride atoms [22,42]. The thin PVDF films made from a melt or a solution have a ferroelectric effect, as dipole moments cancel the crystal and stereochemical conformation structure and additional steps are needed to make these films ferroelectric [41], such as extending the films using PVDF-TrFE instead of PVDF. Ferroelectricity has several common characteristics, including the transitional phase temperature changed Tc(E) with the applied electric field and the spontaneous polarization disappearing above the zero-field Curie point Tc0 [22].

Spontaneous polarization is characterized by a pyroelectric effect, depending on the anisotropic solids temperature. The pyroelectrical coefficient can be measured in principle in two ways: either by manipulating the temperature while the sample size remains constant or let the sample altering its size as a result of thermal expansion. In the second experiment, secondary piezoelectric pyroelectricity is produced [22,26-27]. The major purpose of the slow heating/cooling system and Chynoweth system is to apply pyroelectric measurements. The different of thermal expansion coefficient between the substrate and the polymer makes the film expand and contract just perpendicular to the surface, thus two contributions are included in the calculation in order to measure pyroelectric coefficient $p_3(eff)$ in Equation (1), namely the primary and the secondary effect [22,43]:

$$p3(eff) = \left(\frac{\partial PS}{\partial T}\right)S + \left(\frac{dT33\alpha S3}{SS33}\right) = \left(\frac{I}{A}\right)\left(\frac{\partial T}{\partial t}\right)^{-1} \quad (1)$$

where p3(eff) is denoted as the pyroelectric coefficient, while $S$ referred as strain and $T$ referred as the temperature, dT33 is the stress-free piezoelectric coefficient, αS3 denoted as thermal expansion coefficient, SS33 is the elastic compliance coefficient, $A$ is the surface area, the pyroelectric current is represented by $I$, and the rate of temperature change is expressed by $\partial T/\partial t$. The temperature was controlled by a microprocessor. Figure 2 shows the relationship of pyroelectric coefficients ($P$) towards the heating rate, the concentration of $BaZrO_3$, and temperature [22].

Besides, PVDF is inherently hydrophobic at an angle of water contact greater than 90°, which is about 120° for electrospun mats. The wetting property is, however, normally influenced by the formation on the surface of the film of the dense skin layer, which directly increases the roughness of the surface and also decreases the water contact angle [44-45]. Water contact angles tests have been conducted in order to observe the degree of wettability and the hydrophobicity of the prepared films. Static water contact angles were measured at ambient temperature using the sessile drop method (Data-Physics OCA 20, Data Physics Instruments GmbH Filderstadt). Plus, the water contact angle analysis was performed at least 5 different random spots for each sample. On the same goniometer, dynamic results were recorded. By adjusting the water droplet volume between 2 and 10 μL, the contact angles of the advancing and receding droplets were achieved [45]. The PVDF film naturally has a high-water contact angle value of about 85° to 130° due to its fluorinated composition, which confirm its inherent hydrophobicity [46]

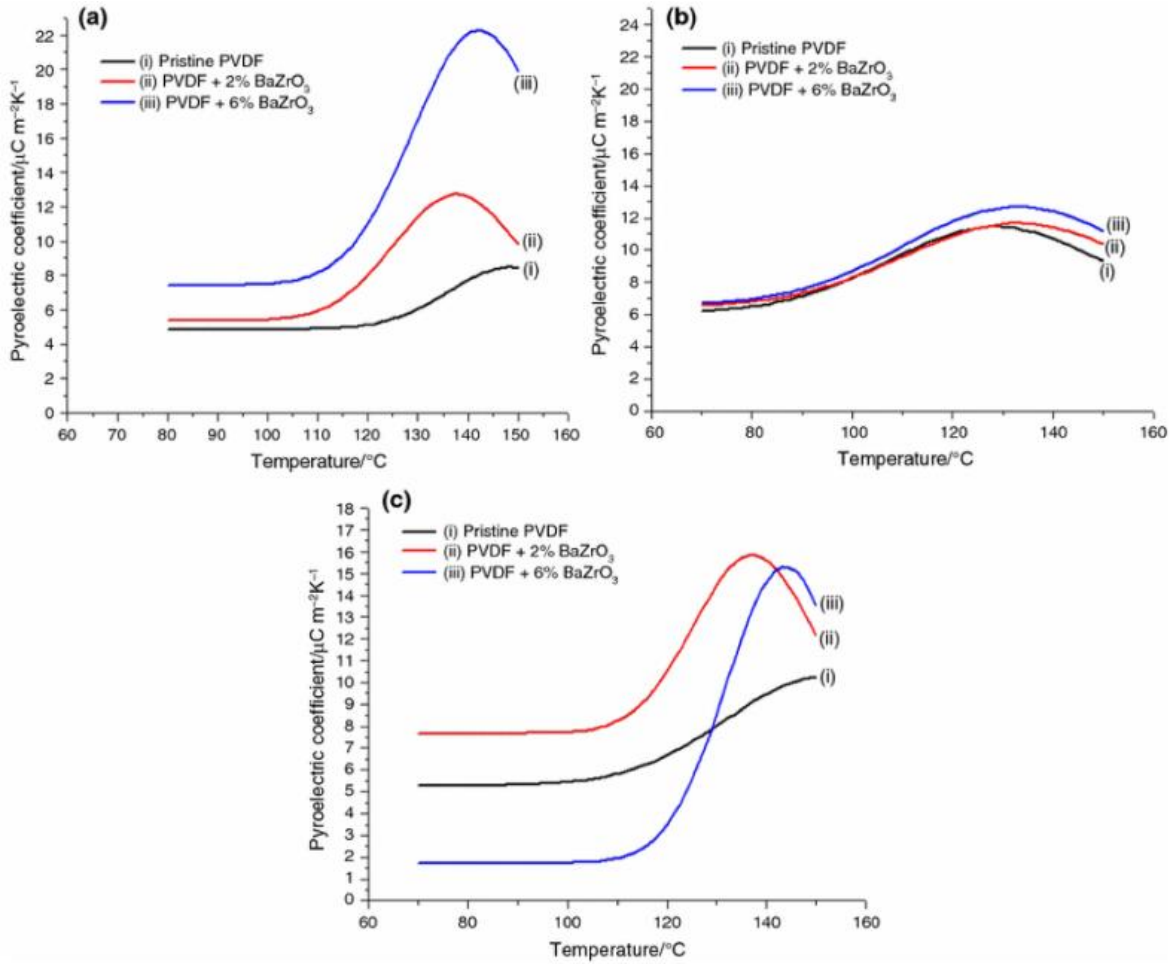


**Fig.2 - Pyroelectric coefficient of PVDF and PVDF nanocomposites towards the temperature of (a) 1 °C/min, (b) 2 °C/min, and (c) 3 °C/min heating rate [22]**

## 5. Application of PVDF in Tissue Engineering

Human body parts such as bone, ligaments, nerve, and cardiac tissue are potentially founded with piezoelectric properties. This special property has attracted to the exploration of PVDF as new smart material by the researchers. A number of scaffolds (membrane, film, hydrogel, composite, etc) have been fabricated using PVDF for a different type of tissue substitutes such as nerve, bone, and cardiac muscle. Young et al. fabricated and studied the potential of the microporous PVDF membranes for the nerve tissue regeneration application by attaching L-lysine covalently on the surface of the PVDF membrane. The collagen from non-mammalian sources could be used to confer bioactivity to PVDF with hemocompatibility to bovine collagen and comparable cell-material interactions [22]. Other than that, the combination of PVDF with polyurethane (PU) produced piezoelectric-excited scaffolds showed enhanced cell migration, adhesion, and secretion, leading to more rapid wound healing than those on the control scaffolds. In vivo assays confirmed with the implantation of these scaffolds in rats and a higher fibrosis level was verified due to the piezoelectric stimulation [18]. The resorption of fibers from the PVDF/chitosan scaffold implanted into endomysium and perimysium has enhanced the adhesion and proliferation of mesenchyme stem cells on their surface. In which this scaffold allocated the great support medium for cell growth with no destruction of chitosan molecules within 45 days after exposed [47].

Other than that, some studies also revealed that the enhancement of the β phase structure leads to excellent piezoelectric properties which successfully supported cardiomyocyte adherence and differentiation compared to the non-piezoelectric scaffold by improving higher alkaline phosphatase activity and earlier mineralization in cells [48-49]. Researchers also have developed nerve guidance conduits or widely known as NGC for peripheral nerve tissue regeneration. The combination of PVDF with graphene oxide (GO) lead to low water contact angle and enhance the absorption of nutrient for better cell proliferation [50]. In vitro cell culture study of modified PVDF with trifluoroethylene (TrFE) show better supporting on Schwann cells and myelination growth compared to neat PVDF scaffold alone [51]. Table 1 summarizes the current application and fabrication techniques of the PVDF scaffold for various tissue engineering applications.

**Table 1 - Application PVDF as various tissue-engineered scaffolds**

| Materials | Fabrication Method | Highlight | Ref |
|---|---|---|---|
| **Nerve Tissue** | | | |
| PVDF / Polycaprolactone (PCL) | Simple cast and annealing-solvent displacement | The PVDF/PCL composite has improved the cell proliferation and differentiation of rat Schwann cells (RSCs) as well as restore the morphological, electrophysiological, and function of 15mm defect rat sciatic nerve model for 4 months. | [52] |
| PVDF/ Gold colloidal nanoparticles (Au NPs) | Electrospinning | The incorporation of Au NPs in the PVDF solution has enhanced the piezoelectricity of electrospun and biocompatible for nerve regeneration as indicated by PC-12 cell-cultured. | [53] |
| PVDF | Electrospinning | Researcher suggests that the fiber alignment affect the growth and differentiation capacities of monkey neural stem cells (NSCs) compared to nonaligned scaffolds. | [54] |
| β-PVDF | - | The results indicate that dynamic stimulation of PVDF by ultrasonic (US) waves activates calcium channels, thus inducing the generation of neurites via a cyclic adenosine monophosphate (cAMP)-dependent pathway which promises a great development of non-invasive neuro regenerative devices. | [55] |
| Molybdenum disulfide ($MoS_2$) / PVDF | Film casting and electrospinning | The 3D composite offers a large surface area for NSC attachment and has a good electrical conductivity that leads to the higher efficiency of NSC differentiation into neural cells. | [56] |
| **Bone and Cartilage Tissue** | | | |
| PVDF–$Ba_{0.9}Ca_{0.1}TiO_3$ / polyvinyl alcohol(PVA) | Electrospinning | The inclusion of $Ba_{0.9}Ca_{0.1}TiO_3$ nanopowder has remarkably improved the protein adsorption, bioactivity, and mechanical characteristics of the PVDF/PVA membrane. It also found that these composite scaffold promising huge potential for bone regrowth based on excellent osteogenic differentiation of mesenchymal stem cells on the membrane. | [57] |
| PVDF | Electrospinning | This study reported that PVDF with negative surface potential has greater potential for bone regeneration due to the enhancement of collagen mineralization that is required for bone tissue growth. | [58] |
| PVDF / Bioglass (BG) | Selective laser sintering | The interconnected porous scaffold formed has great mechanical properties and biological mineralization via Ca and P ions release which have stimulated bone cells growth, | [59] |
| PVDF/GO | Selective laser sintering | GO form strong hydrogen bonding with PVDF lead to improvement of β phase formation and a 97.9% increase in compressive strength of the scaffold which favourable for bone-like cell proliferation. | [60] |
| Polyvinylidene fluoride / hydroxyapatite / β-tricalcium phosphate | Uniaxial pressing | The biocompatible and electrically tuneable biocomposite was developed with large apatite phase growth after 7 days of immersion in simulated body fluid. | [61] |
| PVDF / biphasic calcium phosphate (BCP) | Uniaxial pressing | Inclusion of BCP has improved the apatite formation after 7 days of immersion in SBF with resistance strength reaching 80 MPa which is almost similar to human cartilage/bone tissue strength. | [62] |

| | | | |
|---|---|---|---|
| **Heart / Cardiac Tissue** | | | |
| β-PVDF / poly(methyl methacrylate (PMMA) / hydroxyapatite (HAp) / titanium dioxide ($TiO_2$) (PPHT) | Electrospinning | The prepared nanofiber scaffold is effectively used as a medium for seeded stem cells which can promote cell adhesion, proliferation, and mature into healthy functional cardiac cells with excellent tensile strength which can withstand the vigorous pumping action of heart muscles. | [48] |
| PVDF-TrFe | Electrospinning | The nanofiber electrospun has been validated as a sensor for tissue contraction from as few as $5x10^5$ cardiomyocytes and able to promote differentiation of human-induced pluripotent stem cells into cardiomyocytes. | [63] |
| **Muscle Tissue** | | | |
| PVDF | Film casting and electrospinning | PVDF scaffold showed excellent work by providing electroactive environments for enhancing myogenic differentiation of C2C12 cells as demonstrated through analysis of myotube fusion, length, diameter, number, and maturation index of cells. | [64] |
| PVDF / fibrin | - | Investigate the growth model using the PVDF scaffold showed significant changes in tissue development with training using mechanotransduction as the mechanical property and the smooth muscle was uniformly oriented in higher density. | [65] |
| PVDF / polypyyrole (PPy) | Electrospinning | The electrospun was founded to have a smooth fibrous layer surface with excellent conductivity and low cytotoxicity toward human cells. | [66] |
| **Bladder Tissue** | | | |
| PVDF / chitosan / transforming growth factor beta-1 (TGFβ) | Electrospinning | The scaffold has a smooth arrangement with nanoscale size and a sustainable releasing profile with excellent adipose tissue-derived mesenchymal stem cells (AT-MSCs) proliferation rate. | [67] |
| PVDF / collagen / vascular endothelial growth factor (VEGF) | - | The VEGF-loaded scaffold was found to have better protein adsorption, cell attachment, and viability compared to the neat scaffold. Besides, the study also suggested that these scaffolds have induced angiogenesis and apoptotic related genes during the culture of human umbilical vein endothelial cells and primary bladder smooth muscle cells. | [68] |
| PVDF-mesh | - | 87.5% of treated women felt very well after the surgery treating symptomatic prolapse of the anterior vaginal wall (cystocele) which was measured by the Patient Global Improvement Inventory (PGI-I) scale. | [69] |

## 6. Conclusion

This paper discussed PVDF, one of the most challenging and exciting materials for developing advanced applications due to its uniques characteristic, which offer high constant dielectric, piezoelectric, pyroelectric and ferroelectric effects. The synthesis and β phase formation process was extensively discussed for giving a general overview of the PVDF background. Recent advances have been presented with recent PVDF applications in tissue engineering areas such as nerve, bone, cartilage, heart, muscle, and bladder tissues with a different mode of fabrication techniques. Overall, this review will show this electroactive polymer's massive potential as a future artificial regenerative tissue scaffold material.

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## References

[1] Engel, E., Michiardi, A., Navarro, M., Lacroix, D., & Planell, J.A. (2008). Nanotechnology in Regenerative Medicine: The Materials Side. Trends in Biotechnology, 26(1), 39-47

[2] Fontana, F., Ferreira, M.P.A., Correia, A., Hirvonen, J., & Santos, H.A. (2016). Microfluidics as a Cutting-Edge Technique for Drug Delivery Applications. Journal of Drug Delivery Science and Technology, 34, 76–87

[3] Ma, L., Gao, C., Mao, Z., Zhou, J., Shen, J., Hu, X., & Han, C. (2003). Collagen/Chitosan Porous Scaffolds with Improved Biostability for Skin Tissue Engineering. Biomaterials, 24(26), 4833–4841

[4] Griffith, L.G., & Naughton, G. (2002). Tissue Engineering-Current Challenges and Expanding Opportunities. Science (New York, N.Y.), 295(5557), 100, 9–14

[5] Hamzah, M.S.A., Zulkifli, A.F., Rais, Z.H.A., Razak, S.I.A., & Nayan, N.H.M. (2020). Surface Entrapment of Collagen on Single Layer Polylactic Acid Film Containing Sustainable Drug Delivery Properties for Corneal Tissue Engineering Application. Journal of Sustainability Science and Management, 15(3), 20-35

[6] Spector, J., Stroock, A. D., & Morgan, J. (2018). U.S. Patent No. 9,968,708. Washington, DC: U.S. Patent and Trademark Office

[7] Bardone, E., Brucato, A., Keshavarz, T., Pavia, F.F.C., Rigogliuso, S., Carrubba, V.L., & Brucato, V. (2012). Poly Lactic Acid Based Scaffolds for Vascular Tissue Engineering. Chemical Engineering Transactions, 27, 409–414

[8] Chan, B.P., & Leong, K.W. (2008). Scaffolding in Tissue Engineering: General Approaches and Tissue-Specific Considerations. European Spine Journal, 17(4), 467-479

[9] Kim, M.S., Kim, J.H., Min, B.H., Chun, H.J., Han, D.K., & Lee, H.B. (2011). Polymeric Scaffolds for Regenerative Medicine. Polymer Reviews, 51(1), 23– 52

[10] Hamzah, M.S.A., Abd Razak, S.I., Kadir, M.R.A., Bohari, S.P.M., Nayan, N.H.M., & Anand, J.S.T. (2020). Fabrication and Evaluation of Polylactic Acid/Pectin Composite Scaffold via Freeze Extraction for Tissue Engineering. Journal of Polymer Engineering, 40(5), 421-431

[11] Richardson-Burns, S.M., Hendricks, J.L., Foster, B., Povlich, L.K., Kim, D.H., & Martin, D.C. (2007). Polymerization of the Conducting Polymer Poly (3, 4-Ethylenedioxythiophene) (PEDOT) Around Living Neural Cells. Biomaterials, 28(8), 1539-1552

[12] Chiou, N.R., Lu, C., Guan, J., Lee, L.J., & Epstein, A.J. (2007). Growth and Alignment of Polyaniline Nanofibres with Superhydrophobic, Superhydrophilic and Other Properties. Nature nanotechnology, 2(6), 354

[13] Xu, H., Holzwarth, J.M., Yan, Y., Xu, P., Zheng, H., Yin, Y., Li, S., & Ma, P.X. (2014). Conductive PPY/PDLLA Conduit for Peripheral Nerve Regeneration. Biomaterials, 35(1), 225-235

[14] Ghasemi-Mobarakeh, L., Prabhakaran, M.P., Morshed, M., Nasr-Esfahani, M.H., Baharvand, H., Kiani, S., Al-Deyab, S.S., & Ramakrishna, S. (2011). Application of Conductive Polymers, Scaffolds and Electrical Stimulation for Nerve Tissue Engineering. Journal of Tissue Engineering and Regenerative Medicine, 5(4), e17-e35

[15] Hamzah, M.S.A., Azize, A.H.A., Yusof, S., Noor, S.M., & Nayan, N.H.M. (2019). Electrospinning and Controlled Release Studies of Polyvinylidene Fluoride/Pectin Electrospun Loaded with Crocin as Neuroprotective Membrane Prospect. In Proceeding National Innovation & Invention Competition 2019, 335-339

[16] Mo, X., Sun, B., Wu, T., & Li, D. (2019). Electrospun Nanofibers for Tissue Engineering. In Electrospinning: Nanofabrication and Applications, 719-734

[17] Shao, H., Fang, J., Wang, H., & Lin, T. (2015). Effect of Electrospinning Parameters and Polymer Concentrations on Mechanical-To-Electrical Energy Conversion of Randomly-Oriented Electrospun Poly (Vinylidene Fluoride) Nanofiber Mats. RSC Advances, 5(19), 14345-14350

[18] Ribeiro, C., Correia, D.M., Ribeiro, S., Sencadas, V., Botelho, G., & Lanceros-Méndez, S. (2015). Piezoelectric Poly (Vinylidene Fluoride) Microstructure and Poling State in Active Tissue Engineering. Engineering in Life Sciences, 15(4), 351-356

[19] Alhasssan, Z. A., Burezq, Y. S., Nair, R., & Shehata, N. (2018). Polyvinylidene difluoride piezoelectric electrospun nanofibers: review in synthesis, fabrication, characterizations, and applications. Journal of Nanomaterials, 2018

[20] Sengupta, D., Kottapalli, A.G.P., Chen, S.H., Miao, J.M., Kwok, C.Y., Triantafyllou, M.S. Warkiani, M.E., & Asadnia, M. (2017). Characterization of Single Polyvinylidene Fluoride (PVDF) Nanofiber for Flow Sensing Applications. AIP Advances, 7(10), 105205

[21] Yu, L., Wang, S., Li, Y., Chen, D., Liang, C., Lei, T., Sun, D., Zhao, Y., & Wang, L. (2013). Piezoelectric Performance of Aligned PVDF Nanofibers Fabricated By Electrospinning and Mechanical Spinning. In 2013 13th IEEE International Conference on Nanotechnology (IEEE-NANO 2013) (962-966). IEEE

[22] Ruan, L., Yao, X., Chang, Y., Zhou, L., Qin, G., & Zhang, X. (2018). Properties and Applications of the β Phase Poly(vinylidene fluoride). Polymers,10(3), 228

[23] Li, Y., Liao, C., & Tjong, C. (2019). Electrospun Polyvinylidene Fluoride-Based Fibrous Scaffold with Piezoelectric Characteristic for Bone and Neural Tissue Engineering. Nanomaterial, 9, 952
[24] Wang, S., & Li, Q. (2018). Design, Synthesis and Processing of PVDF-Based Dielectric Polymers. IET Nanodielectrics, 1(2), 80-91.
[25] Ameduri, B. (2009). From Vinylidene Fluoride (VDF) to the Applications of VDF-Containing Polymers and Copolymers: Recent Developments and Future Trends. Chemical Reviews, 41(17), 6632-6686.
[26] Banerjee, S., Ladmiral, V., Debuigne, A., Detrembleur, C., Poli, R., & Ameduri, B. (2018). Organometallic-Mediated Radical Polymerization of Vinylidene Fluoride. Angewandte Chemie International Edition, 57(11), 2934– 2937.
[27] Falireas, P.G., Ladmiral, V., Debuigne, A., Detrembleur, C., Poli, R., & Ameduri, B. (2019). Straightforward Synthesis of Well-Defined Poly (vinylidene fluoride) and Its Block Copolymers by Cobalt-Mediated Radical Polymerization. Macromolecules, 52(3), 1266-1276.
[28] Doll, W. W., & Lando, J. B. (1970). The Polymorphism of Poly (Vinylidene Fluoride) IV. The Structure of High-Pressure-Crystallized Poly (Vinylidene Fluoride). Journal of Macromolecular Science, Part B, 4(4), 889-896.
[29] Scheinbeim, J., Nakafuku, C., Newman, B.A., & Pae, K D. (1979). High-Pressure Crystallization of Poly (Vinylidene Fluoride). Journal of Applied Physics, 50(6), 4399-4405.
[30] Yang, D., & Chen, Y. (1987). β-Phase Formation of Poly (Vinylidene Fluoride) from the Melt Induced by Quenching. Journal of Materials Science Letters, 6(5), 599-603.
[31] Gradys, A., Sajkiewicz, P., Adamovsky, S., Minakov, A., & Schick, C. (2007). Crystallization of Poly (Vinylidene Fluoride) During Ultra-Fast Cooling. Thermochimica Acta, 461(1-2), 153-157.
[32] Gregorio Jr, R., & Borges, D. S. (2008). Effect of Crystallization Rate on the Formation of the Polymorphs of Solution Cast Poly (Vinylidene Fluoride). Polymer, 49(18), 4009-4016.
[33] Mohammadi, B., Yousefi, A.A., & Bellah, S.M. (2007). Effect of tensile Strain Rate and Elongation on Crystalline Structure and Piezoelectric Properties of PVDF Thin Films. Polymer Testing, 26(1), 42-50.
[34] Guo, H., Zhang, Y., Xue, F., Cai, Z., Shang, Y., Li, J., Chen, Y., Wu, Z., & Jiang, S. (2013). In-Situ Synchrotron SAXS and WAXS Investigations on Deformation and A–B Transformation of Uniaxial Stretched Poly (Vinylidene Fluoride). CrystEngComm, 15(8), 1597-1606.
[35] Tang, C. W., Li, B., Sun, L., Lively, B., & Zhong, W. H. (2012). The Effects of Nanofillers, Stretching and Recrystallization on Microstructure, Phase Transformation and Dielectric Properties in PVDF Nanocomposites. European Polymer Journal, 48(6), 1062-1072.
[36] Ye, H.J., Yang, L., Shao, W.Z., Sun, S.B., & Zhen, L. (2013). Effect of Electroactive Phase Transformation on Electron Structure and Dielectric Properties of Uniaxial Stretching Poly (Vinylidene Fluoride) Films. RSC Advances, 3(45), 23730-23736.
[37] Zheng, J., He, A., Li, J., & Han, C. C. (2007). Polymorphism Control of Poly (Vinylidene Fluoride) Through Electrospinning. Macromolecular Rapid Communications, 28(22), 2159-2162.
[38] Lei, T., Yu, L., Zheng, G., Wang, L., Wu, D., & Sun, D. (2015). Electrospinning-Induced Preferred Dipole Orientation in PVDF Fibers. Journal of Materials Science, 50(12), 4342-4347.
[39] Ribeiro, C., Sencadas, V., Ribelles, J.L.G., & Lanceros-Méndez, S. (2010). Influence of Processing Conditions on Polymorphism and Nanofiber Morphology of Electroactive Poly (Vinylidene Fluoride) Electrospun Membranes. Soft Materials, 8(3), 274-287.
[40] Beringer, L. T., Xu, X., Shih, W., Shih, W. H., Habas, R., & Schauer, C. L. (2015). An electrospun PVDF-TrFe fiber sensor platform for biological applications. Sensors and Actuators A: Physical, 222, 293-300.
[41] Naber, R.C., Asadi, K., Blom, P.W., de Leeuw, D.M., & de Boer, B. (2010). Organic Nonvolatile Memory Devices Based on Ferroelectricity. Advanced Materials, 22(9), 933-945.
[42] Kepler, R. G., & Anderson, R. A. (1992). Ferroelectric Polymers. Advances In Physics, 41(1), 1-57.
[43] Lines, M.E., & Glass, A.M. (1997). Principles and Applications of Ferroelectrics and Related Materials; Oxford University Press: Oxford, UK.
[44] Li, K., Hou, D., Fu, C., Wang, K., & Wang, J. (2019). Fabrication of PVDF Nanofibrous Hydrophobic Composite Membranes Reinforced with Fabric Substrates via Electrospinning for Membrane Distillation Desalination. Journal of Environmental Sciences, 75, 277-288.
[45] Moradi, R., Karimi-Sabet, J., Shariaty-Niassar, M., & Koochaki, M. (2015). Preparation and Characterization of Polyvinylidene Fluoride/Graphene Superhydrophobic Fibrous Films. Polymers, 7(8), 1444-1463.
[46] Leenaerts, O., Partoens, B., & Peeters, F.M. (2009). Water on Graphene: Hydrophobicity and Dipole Moment Using Density Functional Theory. Physical Review B, 79(23), 235440.
[47] Wu, L., Wang, H., Xu, T.W., & Xu, Z.L. (2017). Polymeric Membranes. In Membrane-Based Separations in Metallurgy (297-334). Elsevier.
[48] Arumugam, R., Srinadhu, E. S., Subramanian, B., & Nallani, S. (2019). β-PVDF Based Electrospun Nanofibers–A Promising Material for Developing Cardiac Patches. Medical Hypotheses, 122, 31-34.
[49] Yuan, H., Lei, T., Qin, Y., He, J.H., & Yang, R. (2019). Design and Application of Piezoelectric Biomaterials. Journal of Physics D: Applied Physics, 52(19), 194002.

[50] Abzan, N., Kharaziha, M., & Labbaf, S. (2019). Development of Three-Dimensional Piezoelectric Polyvinylidene Fluoride-Graphene Oxide Scaffold by Non-Solvent Induced Phase Separation Method for Nerve Tissue Engineering. Materials & Design, 167, 107636.
[51] Wu, S.C. (2018). Aligned Fibrous PVDF-TrFE Scaffolds with Schwann Cells Support Neurite Extension and Myelination In Vitro. Journal of Neural Engineering, 15(5), 056010.
[52] Cheng, Y., Xu, Y., Qian, Y., Chen, X., Ouyang, Y., & Yuan, W.E. (2020). 3D Structured Self-Powered PVDF/PCL Scaffolds for Peripheral Nerve Regeneration. Nano Energy, 69, 104411.
[53] Motamedi, A.S., Mirzadeh, H., Hajiesmaeilbaigi, F., Bagheri-Khoulenjani, S., & Shokrgozar, M.A. (2017). Piezoelectric Electrospun Nanocomposite Comprising AuNPs/PVDF for Nerve Tissue Engineering. Journal of Biomedical Materials Research Part A, 105(7), 1984-1993.
[54] Lins, L.C., Wianny, F., Livi, S., Dehay, C., Duchet-Rumeau, J., & Gérard, J.F. (2017). Effect of Polyvinylidene Fluoride Electrospun Fiber Orientation on Neural Stem Cell Differentiation. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 105(8), 2376-2393.
[55] Hoop, M., Chen, X.Z., Ferrari, A., Mushtaq, F., Ghazaryan, G., Tervoort, T., Poulikakos, D., Nelson, B., & Pané, S. (2017). Ultrasound-Mediated Piezoelectric Differentiation of Neuron-Like PC12 Cells on PVDF Membranes. Scientific reports, 7(1), 1-8.
[56] Wang, S., Qiu, J., Guo, W., Yu, X., Nie, J., Zhang, J., Zhang, X., Liu, Z., Mou, X., Li, L., & Liu, H. (2017). A Nanostructured Molybdenum Disulfide Film for Promoting Neural Stem Cell Neuronal Differentiation: Toward a Nerve Tissue-Engineered 3D Scaffold. Advanced Biosystems, 1(5), 1600042.
[57] Ahmadi, N., Kharaziha, M., & Labbaf, S. (2019). Core–Shell Fibrous Membranes of PVDF–$Ba_{0.9}Ca_{0.1}TIO_3$/PVA with Osteogenic and Piezoelectric Properties for Bone Regeneration. Biomedical Materials, 15(1), 015007.
[58] Szewczyk, P.K., Metwally, S., Karbowniczek, J.E., Marzec, M.M., Stodolak-Zych, E., Gruszczyński, A., Bernasik, A., & Stachewicz, U. (2018). Surface-Potential-Controlled Cell Proliferation and Collagen Mineralization on Electrospun Polyvinylidene Fluoride (PVDF) Fiber Scaffolds for Bone Regeneration. ACS Biomaterials Science & Engineering, 5(2), 582-593.
[59] Shuai, C., Huang, W., Feng, P., Gao, C., Gao, D., Deng, Y., Wang, Q., Wu, P., & Guo, X. (2017). Nanodiamond Reinforced Polyvinylidene Fluoride/Bioglass Scaffolds for Bone Tissue Engineering. Journal of Porous Materials, 24(1), 249-255.
[60] Shuai, C., Zeng, Z., Yang, Y., Qi, F., Peng, S., Yang, W., He, C., Wang, G., & Qian, G. (2020). Graphene Oxide Assists Polyvinylidene Fluoride Scaffold to Reconstruct Electrical Microenvironment of Bone Tissue. Materials & Design, 190, 108564.
[61] Bonadio, T.G., Freitas, V.F., Tominaga, T.T., Miyahara, R.Y., Rosso, J.M., Cótica, L.F., Baesso, M.L., Weinand, W.R., Santos, I.A., Guo, R., & Bhalla, A.S. (2017). Polyvinylidene Fluoride/Hydroxyapatite/B-Tricalcium Phosphate Multifunctional Biocomposite: Potentialities for Bone Tissue Engineering. Current Applied Physics, 17(5), 767-773.
[62] Silva, L.M., Rosso, J.M., Bonadio, T.G.M., Silva, D.M., Dias, G.S., Weinand, W.R., Tominaga, T.T., Miyahara, R.Y., Cótica, L.F., Santos, I.A., & Freitas, V.F. (2018). On Mechanical Properties and Bioactivity of PVDF-BCP Composites. Cerâmica, 64(371), 359-366.
[63] Adadi, N., Yadid, M., Gal, I., Asulin, M., Feiner, R., Edri, R., & Dvir, T. (2020). Electrospun Fibrous PVDF-TrFe Scaffolds for Cardiac Tissue Engineering, Differentiation, and Maturation. Advanced Materials Technologies, 5(3), 1900820.
[64] Ribeiro, S., Gomes, A.C., Etxebarria, I., Lanceros-Méndez, S., & Ribeiro, C. (2018). Electroactive Biomaterial Surface Engineering Effects on Muscle Cells Differentiation. Materials Science and Engineering: C, 92, 868-874.
[65] Dương, M.T., Seifarth, V., Artmann, A., Artmann, G.M., & Staat, M. (2018). Growth Modelling Promoting Mechanical Stimulation of Smooth Muscle Cells of Porcine Tubular Organs in a Fibrin-PVDF Scaffold. In Biological, Physical and Technical Basics of Cell Engineering (209-232). Springer, Singapore.
[66] Dias, J.C.R. (2018). Development of ionic electroactive polymers for artificial muscle applications. Doctoral Thesis, University of Minho.
[67] Ardeshirylajimi, A., Ghaderian, S.M.H., Omrani, M.D., & Moradi, S.L. (2018). Biomimetic Scaffold Containing PVDF Nanofibers with Sustained TGF-B Release in Combination with AT-MSCs for Bladder Tissue Engineering. Gene, 676, 195-201.
[68] Mokhames, Z., Rezaie, Z., Ardeshirylajimi, A., Basiri, A., Taheri, M., & Omrani, M.D. (2020). VEGF-Incorporated PVDF/Collagen Nanofibrous Scaffold for Bladder Wall Regeneration and Angiogenesis. International Journal of Polymeric Materials and Polymeric Biomaterials, 1-9.
[69] Barski, D., Arndt, C., Gerullis, H., Yang, J., Boros, M., Otto, T., & Kolberg, H.C. (2017). Transvaginal PVDF-Mesh for Cystocele Repair: A Cohort Study. International Journal of Surgery, 39, 249-254.