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Review Article

Medical Uses of Synthetic Piezoelectric Polymers; 2020-2021 Overview

Hilal Yilmaz*

* *Department of Bioengineering Laboratory of Cell Culture and Tissue Engineering, Yildiz Technical University, 34220, Istanbul, Turkey*

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*Corresponding author: Hilal Yilmaz
E-mail: hilaltoptas44@gmail.com

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Abstract

Smart materials that can reverse one or more of their functional or structural properties according to the external stimulus are the most trending topic of our time. Many fields, including medicine, benefit from smart polymers, which are one of these smart materials. In this review, we will talk about synthetic piezoelectric polymers, which are members of the smart polymer family, and give an overview of their use in different medical fields and examine the points where they are most popular. In this study, our aim is to collect only synthetic piezoelectric polymers in a text and sample these most up-to-date studies in detail, unlike the reviews written in this field.

Keywords: Smart materials, Piezoelectric materials, Synthetic piezoelectric polymers.

1. Introduction

Smart materials are the most trending topic of materials science, which is advancing in line with the rapid technological developments of our age. Smart materials are generally called materials that can reverse one or more of their functional or structural properties according to the changes in environmental conditions and activate the systems in which they are located (1). To stimulate intelligent materials;

- External stimuli, physical (temperature, light, electric or magnetic field),
- Chemical (pH),
- Mechanical stimuli (stress and strain) are used (2).

Some of those smart materials are shape memory alloys, thermo-piezoelectric materials, photovoltaic materials, magnetically intense materials, piezoelectric materials, electro-logical fluxes, light-emitting diodes, color-changing materials, and smart polymers (3, 4). Among smart materials, piezoelectric materials are the most commonly used due to their wide bandgap, rapid electromechanical responses, relatively low power requirements, and high productive forces. Today, there are many piezoelectric materials already used in medicine. One of them is piezoelectric polymers. Polymers are more desirable than inorganic materials. Because they are light, inexpensive, mechanically and electrically durable. They have excellent compatibility with other organic and inorganic materials for the development of multifunctional hybrid systems. Some polymers are biocompatible, and some are biodegradable (5-7). Increased advances in materials science and engineering enable the improvement and optimization of smart materials, and especially smart polymer materials, for a greater number of applications (8). Smart polymers are macromolecules that can rapidly and reversibly switch from hydrophilic to hydrophobic microstructure. These transitions are triggered by minor changes in their environment. This type of material greatly affects the medical field and is encountered in almost every discipline of medicine in today's technology. Piezoelectric polymers have been known for over 40 years. They are included in the class of both smart materials (9) and electro-active materials (10). Smart materials that react differently from traditional materials when a specific stimulus is applied are generally called piezoelectric materials. The ability to generate electrical signals in response to mechanical stress is recognized as piezoelectricity, the ability to generate electrical signals in response to a temperature change is known as pyro-electricity and the ability to respond repeatedly by reversing external electrical fields is known as Ferroelectricity (11). Piezoelectric materials are materials that expand or contract in an electrical field or generate an electrical charge when pressure is applied (12). The word Piezo is of Latin origin and means applying pressure. The name "piezoelectric" was given to these materials by Hankel in 1881. For a material to exhibit piezoelectric properties, it needs basic properties such as having a crystal lattice structure and no symmetry center. Piezoelectricity, on the other hand, is the ability to generate electricity in direct proportion to the force applied to crystalline objects from the outside. While some materials (biological and crystalline) exhibit spontaneous piezoelectricity, some materials (ceramic, synthetic polymer, and their composites) exhibit piezoelectricity only when processed under certain conditions. With piezoelectric materials, forces and strains with frequencies between hertz and megahertz, movements at micrometer levels, forces between millinewtons and kilonewtons can be detected with high sensitivity (13). Biomaterials with piezoelectric properties are generally divided into four classes (14). These are:

- Piezoelectric crystals that exist in nature (such as quartz, Rochelle salt),
- Piezoelectric ceramics (titanates, lead-based and lead-free ceramics),

- Piezoelectric polymers (natural and synthetic piezoelectric polymers)
- Piezoelectric composites

These materials can be found naturally in nature, or they can also be obtained synthetically based on ceramics such as PZT (lead-titanate-zirconate), barium titanate. Synthetically obtained ones are more useful than natural piezo-materials in terms of physical, chemical, mechanical, and piezoelectric properties; they are more stable chemically, more resistant to moisture and atmospheric conditions. They can be easily adapted to particular applications, providing easy and inexpensive production for applications requiring complex geometry or large volume (13). Natural crystals and piezoelectric ceramics cannot be produced in large surface areas or complex shapes because they exhibit the brittle properties of ceramic materials. For this reason, searches for polymers with piezoelectric properties, which are believed to be a better alternative to these materials, have been started and the first polymer discovered is polyvinylidene fluoride (PVDF) (13). The properties of piezoelectric polymers differ from inorganic crystals due to their flexible processing advantages. Mechanically, piezoelectric polymers have high strength and high impact resistance, unlike inorganic materials. In the literature, it has recently found a lot of work, especially in the medical field. In this review, we will closely examine synthetic piezoelectric polymers and their composites and provide information about their use in many different medical fields between 2020 and 2021.

2. Piezoelectric Polymers

Piezoelectric polymers are polymers that can generate electric charges on the surface under pressure/strain thus convert mechanical energy into electrical energy (15). As it is known, polymers consist of two different structures: amorphous region and crystalline region. The amount of crystalline region in the polymer structure affects the piezoelectric property. While the amount of crystalline region in the polymer determines the boiling point of the polymer, the amount of amorphous region is also effective on the glassy transition temperature and mechanical properties. Semi-crystalline molecular polar pairs are locked within amorphous regions. Mechanically, polymers have higher strength and higher impact resistance than inorganic materials. The properties of piezoelectric polymers differ from inorganic crystals because they have the advantage of processing flexibility (16).

We can list the structural properties of piezoelectric polymers as follows:

• The presence of permanent molecular dipoles,

• The ability to align or orient molecular dipoles,

• The ability to maintain alignment after aligning and

• The ability of the material to be exposed to large strains when forced mechanically (17).

Although these materials are used as part of many devices in the medical field, the first use of piezoelectric materials to correct bone damage emerged in the 1970s, while the first piezoelectric polymer used in this field is PVDF with the piezoelectric coefficient closest to the bone (8pC/N). While choosing this material, it was inspired by the biological piezoelectric character of bone (18). It has been observed that this biomaterial actively stimulates the tissue with desired electrical and mechanical responses. Piezoelectric polymers have demonstrated simple processing, flexibility, and better physical properties than various types of piezoelectric materials, making these materials a better choice for a variety of

applications. PLLA, PHB, PVDF, some polyamides, and their copolymers are the materials with the greatest piezo responses (19). Some polymers can be given piezoelectric properties by undergoing some processes (20), and we will only examine synthetic piezoelectric polymers (Table1) in this review. Piezoelectric coefficients are defined by double sub-numbers. The first subscript shown indicates applied voltage/charge generated in the direction of the respective electric field; the second subscript indicates the direction of the mechanical stress/strain (21). The piezoelectric coefficients are d_{33}, d_{31}, d_{15} etc. The coefficient d_{33} measures the deformation in the same direction (polarization axis) as the induced potential, whereas d_{31} refers to the response applied perpendicular to the force polarization axis.

Table 1. Synthetic piezoelectric polymers / copolymers.

SYNTHETİC PİEZOELECTRİC POLYMERS / COPOLYMERS	Piezoelectric coefficient for (d31)	REF.
P(VDF)	8 -22 pC/N	(22)
P(VDF-TRFE)	12 pC/N	(22)
P(VDF-HFP)	30 pC/N	(22)
P(VDF-CTFE)	6 pC/N	(23)
PHA	-	
P(HBV)	1.3 pC/N	(24)
P(3HB-co-4HB)	-	
P(4HB)	-	
PLA	10 pC/N	(25)
PLLL	1.58 pC/N	(26)
Nylon-11	3 pC/N at 25°C	(27)
Polyurea	10 pC/N	(28)

2.1. Polyvinylidene Fluoride, P(VDF)

Polyvinylidene fluoride (PVDF) was the first polymer whose piezoelectric property was discovered (29). PVDF is known as a great biocompatible thermoplastic polymer. It has high chemical and physical resistance. However, it tends to degrade when exposed to an excessive alkaline status (30). Polyvinylidene fluoride is a synthetic semi-crystalline long-chain polymer with a repeat unit -CF2-CH2-. PVDF is inherently polar, as hydrogen atoms are positively charged and fluoride atoms are negatively charged compared to carbon atoms (29). However, the net polar moment of the material in its original form is zero due to the random orientation of the individual crystallites (31). It is the best-known piezoelectric polymer with its piezoelectric coefficient and behavior. Therefore, it is the best applicable polymer of piezoelectric response materials for specific applications (32). The piezoelectric properties of this polymer are between 8 and 22 for d_{31} (pC/N) PVDF and between 24 and 34 for d_{33} (pC/N) PVDF. PVDF exhibits impressive polymorphism. There are at least five crystal phases, α, β, γ, δ and ε (22). β-phase PVDF is considered the optimal stimulation for electrical response applications since it carries the best piezoelectric coefficients (33). In tissue engineering studies with this material, it has been reported that it has a positive effect on adhesion, differentiation, and proliferation of the cell (19). In many medical studies, it has been reported that composites are more effective than their plain form (34). PVDF has important electro-active properties as a biocompatible material. The piezoelectric effect is an electric potential brought about by the induction of mechanical stress. It is known that the positive or negative surface load carried by PVDF films affects the hydrophobicity of the samples and develops diversity in the absorbed extracellular matrix protein structure. In this way, it is ensured that the adhesion is controlled for stem cell differentiation (19). The three copolymers of PVDF are poly(vinylidene fluoride-co-trifluoroethylene) (P(VDFTrFE)), poly(vinylidene fluoride-co-

hexafluoropropylene) (P(VDF-HFP)) (35) and poly(vinylidene) fluoride-chlorotrifluoroethylene) (P(VDF-CTFE)). In addition, the surface morphologies of polymers and copolymers are generally different in terms of spherulite size and organization (23). Due to their high piezoelectric properties, these polymers and their copolymers are used in many technological fields such as biomedicine, biosensor production, smart scaffold production, and filtration membrane production (22).

2.1.1. Poly (Vinylidene Fluoride-co-Trifluoroethylene), P(VDF-TRFE)

It is a copolymer of vinylidene fluoride (VDF) and trifluoroethylene (TrFE). It has been shown to have the highest piezoelectric coefficient (30 pC/N) among copolymers (36). It affects cell adhesion and cell proliferation (37). It can regenerate different tissue types (34, 37-39). The piezoelectric properties of this polymer are 12 for d_{31} (pC/N) and 38 for d_{33} (pC/N) (22).

2.1.2. Poly (Vinylidene Fluoride-Cohexafluoropropene), P(VDF-HFP)

P(VDF-HFP) has a lower crystallinity than PVDF. It is also a semi-crystalline polymer with strong ferroelectric properties when the samples are prepared in casting solvents. The inclusion of hexafluoropropylene (HFP) in the main structure of PVDF leads to an increase in the content of fluorine atoms, increasing the hydrophobicity and solubility of this copolymer (40). The piezoelectric properties of this polymer are 30 for d_{31} (pC/N) and 24 for d_{33} (pC/N) (22). P(VDF-HFP), which shows high electrochemical stability, is a very suitable material for the decomposition of lithium salts with its high dielectric constant (41, 42). It is thermally stable up to a temperature of about 475 C (43). It affects cell adhesion and cell proliferation (34). It is used in smart clothing technology (44).

2.1.3. Poly (Vinylidene Fluoride Cochlorotrifluoroethylene), P(VDF-CTFE)

P(VDF-CTFE) is a copolymer originally designed for wire and cable applications where high flexibility, high elongation, and cold impact resistance are required. Membranes prepared from this polymer have limited use in drinking and wastewater treatment areas due to their hydrophobic structure despite their high chemical, thermal stability, and good mechanical properties. However, those in the health field are also promising (45, 46). The piezoelectric properties of this polymer are 6 for d_{31} (pC/N) and 140 for d_{33} (pC/N) (23).

2.2. Polyhydroxyalkanoates, PHA

PHAs are polyesters of various hydroxy alkanoates synthesized by many gram-positive and gram-negative bacteria belonging to at least 75 different genera. These polymers accumulate intracellular at levels as high as 90% of the cell dry weight under the conditions of nutritional stress and act as a carbon and energy reserve (47). Being a very good biodegradable polymer, PHAs are a natural byproduct of bacteria as a carbon/energy complex. They are biodegradable and biocompatible, non-toxic, insoluble in water (hydrophobic), inert, highly stable in air, piezoelectric, thermoplastic, and elastomeric (48). PHAs has a wide range of physical properties, whether they occur naturally or engineered polyester. When PHA chains crystallize following the melting of bulk materials, spherulites usually form; these crystals are deposited in the cytoplasmic membrane of Escherichia coli as twisted low molecular weight poly(3-hydroxybutyrate) (P3HB)**).** It is also a membrane component in yeasts, plants, and animals. PHAs are generally divided into two groups. Short-chain PHAs have 3–5 carbon atoms in monomeric units, while alternatively, medium-chain PHAs have 6–18

carbon atoms in monomeric units. Today, it is also used in the medical field due to many of its properties (49). P3HB as well as poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (P (3HB-co-3HV)) are the most common PHAs (19).

2.2.1. Poly-3-Hydroxybutyrate-3-Hydroxy Valerate, P(HBV)

PHBV is a member of the PHA family, which was first produced and commercialized as "Biopol" in 1983 (50). PHBV can be synthesized by its bacterial counterparts *Ralstonia eutropha* and *Paracoccus denitrificans* as energy storage compounds under limited growth conditions (51). In addition, PHBV is thermoplastic and can be shaped by thermal injection molding, while its poor thermo-stability increases processing difficulty (52). It has a long degradation time. It has a piezoelectric coefficient close to that of human bone (1.3 pC/N).

2.2.2. Poly (3-Hydroxybutyrate-Co-4-Hydroxybutyrate), P(3HB-co-4HB)

P(3HB-co-4HB) is a biodegradable polymer from the PHA group with properties similar to synthetic thermoplastics. This polymer can be adapted by changing its composition to obtain a range of materials with different mechanical and functional properties, from hard crystalline plastics to elastic rubbers (53). The *in vivo* degradation kinetics of P(3HB-co-4HB) is relatively rapid compared to other PHAs and can be modulated by varying the 4-hydroxybutyrate fraction (54). It is an FDA-approved biomaterial. As a result, P(3HB-co-4HB) has been applied in a wide range of biomedical fields such as tissue engineering, wound healing, and drug release (55).

2.2.3. Poly (-4-Hydroxybutyrate), P(4HB)

P4HB is a widely used PHA. It is a polyhydroxyalkanoate developed as an absorbable biomaterial for medical applications. It was first developed in the early 1990s by researchers at the Massachusetts Institute of Technology (56). It has received FDA approval for use in several clinical applications. This biopolymer has features that expand the field of biomaterial design and enable the development of new and improved absorbable medical products. P4HB is a strong thermoplastic polymer and has significantly greater flexibility than other synthetic absorbable polymers such as polyglycolide and poly-L-lactide. P4HB is typically melt spun and drawn into filaments at temperatures between 180 and 21°C for a variety of applications, but higher molecular weight P4HB (>800 kDa) may require higher temperatures for processing due to its higher melting viscosity (57). Some of the products under development using P4HB are vascular grafts, stents, patches, and sutures (53). It is also being evaluated for controlled-release drug delivery applications involving a variety of therapeutic chemicals and drugs, particularly thermally sensitive ones (58).

2.3. Poly (L-Lactic Acid), PLLL

Poly (lactic acid) (PLA) is a frequently used biomaterial. In addition to low density and processing power, it has properties such as corrosion resistance, elastomeric behavior, and versatility. Its piezoelectric property is known as approximately 10 pC/N (25). Due to its bioresorption, low toxicity, degradation, biocompatibility, and beneficial mechanical performance, its work in the field of medicine continues to increase day by day. PLA; It has linear forms of polyester stereoisomers, including poly(l-lactic acid) (PLLA), poly(d-lactic acid) (PDLA), and poly(d, l-lactic acid) (PDLLA). PLLA has optical activity properties and PDLA is available as its optical isomer. The piezoelectric effects of extruded PLLA and PDLA have been studied in the past using rods and films. It is because there is a noticeable increase in the chain alignment of PLA polymers caused by strain. PLLA is a promising piezoelectric polymer for applications

in neural healing as well as bone regeneration and growth because it can exhibit the electro-response caused by stress (19) since it is produced from biomass, it is used in many studies and is widely available commercially (59). Especially due to its similarity to extracellular matrix (ECM), it has found widespread use as a biomaterial in tissue engineering studies (60). It supports tissue growth, supports cell growth (61), supports neurite elongation (63) is effective in cell differentiation (62). The piezoelectric coefficient of PLLL is known as 1.58 pC/N (26).

2.4. Polyamides

Polyamides also referred to as nylon, are high polymers that contain amide repeat linkages in the polymer backbone. Generally, they are characterized as solid, translucent, semi-crystalline polymers that are moderately low cost and can be easily manipulated commercially through melt processing (64). Polyamides and polypeptides have piezoelectricity due to odd-numbered nylons and peptide (CONH) bonds, respectively (32), and due to the alignment of the high dipole moment of the amide group in the periodic array of crystalline regions of the polymer during the process called poling. Piezoelectric polarization proceeds as a result of stress-induced internal rotation of peptide bonds (65). This property was observed in nylon-11, nylon-9, nylon-7, and nylon-5 (66). Odd-number nylons contain even methylene groups and an amide group in each monomer unit (27). Odd-number nylons have a powerful piezoelectric effect with piezoelectric strain and strain coefficients d_{31} and e_{31}, and these materials form copolymers only with poly (vinylidene fluoride) (67). The piezoelectric coefficient for nylon (d_{31}) is 3pC/N at 25 °C and 14pC/N at 107 °C (27).

2.5. Polyureas

Aliphatic polyureas have higher flexibility than their molecular chains due to their structure. Similar to polyamides, the orientation of its polarization plays a major role in stabilizing hydrogen bonds. Polyureas with an odd number of methyl groups usually exhibit polarization above zero. Aliphatic polyureas are piezoelectric because they have an odd number of methyl groups. Their thermal stability and piezoelectric coefficient are highly dependent on the polarization temperature (typically 70–150 ◦C) but are lower than aromatic polyureas (68). The piezoelectric coefficient d_{31} is 10 pC/N (27). Its potential to be used in drug release systems (69), magnetic imaging (70), and in different fields of medicine is promising (71).

3. Piezoelectric Polymers In Medicine

In the beginning part, we have tried to explain the subject by talking about piezoelectric materials and their polymers. In this section, we will talk about the smart systems made in very different medical fields with these piezoelectric polymers, in general. It should be noted that smart materials do not consist only of piezoelectric polymers and their copolymers. They are also highly technologically intelligent systems, including insulating polymers and carbon nanomaterials. These materials have recently become an area that has developed intensively, as shown in numerous scientific publications. Bioelectricity has become a very important part of the living being, playing a vital role in every event that will take place throughout its life, from the first stage of its formation. Endogenous electric fields can affect cellular processes such as chemotaxis, migration, proliferation, and differentiation of cells. These areas affect cell division, intracellular communication, neuronal activities, mechanic-transduction, ion transport, and bone and epithelial healing. The electric field provides electrotherapy for accelerated wound healing, deep brain stimulation, tissue

regeneration, improved musculoskeletal system conditions, and bone fracture healing. However, external devices or electrodes are used to deliver low-level electrical currents through the skin (14). At the beginning of the 18th century the use of electrostatic charge for the treatment of skin lesions was defined, and in 1983 electrical potentials ranging from 10 to 60 mV were measured depending on the position of the human body, and it was understood that electric fields and potentials produce significant effects on cells. It has been proven to enable small electric fields to move and migrate directionally in different cell types (cornea, epithelial cells). These domains act as dynamic remodelers for the signaling pathways and functional requirements of cells.

In addition to therapeutic advantages, there is a high need for intelligent biomaterials that can comfortably generate and transmit bioelectrical signals similar to local tissues for appropriate physiological functions. Piezoelectric materials can generate electrical signals in response to applied stress. They can also stimulate signaling pathways and thus increase tissue regeneration at the impaired site. Piezoelectric scaffolds can function as sensitive mechanoelectrical transduction systems (12). They can modulate the phenotypes of vascular endothelial cells, regenerate nerve fibers. In addition, they have been widely used in orthopedic applications as they provide in vivo ligament healing (72). There are extensive studies on the piezoelectric properties of bone and other biological materials. Piezoelectricity plays an important role in the living tissue and various physiological events. Piezoelectricity is therefore found in different parts of the human body such as bone, tendon, cartilage, skin, dentin, collagen, deoxyribonucleic acids (DNA), and possibly in cell membranes. Living cells exhibit many characteristics of electrical systems; they produce electromotor force, regulate their potential difference when necessary, use resistances that change serially or in parallel, control and correct the current flow and store the load. For example, while there is an electrical voltage along the plasma membrane, the inside of the cell remains more negative from the outside (72). In summary, piezoelectric synthetic polymers are used in all fields of medicine, including the human body. In this section, we will examine their use in many medical fields in general in 2020-2021.

3.1. Smart Clothes

In this section, the use of synthetic piezoelectric polymers for medical purposes in textiles between 2020 and 2021 was examined (Table 2). With the latest technological developments, the demand for new and exciting properties of textile products has increased, various sensor and actuator structures have been reported by incorporating electro-active fibers into fabrics (73). The ideal comfort-wearing device is like fabric and can be incorporated into clothing without problems (74). In particular, piezoelectric sensors combined with fibers provide biometric monitoring/detection (73) and flexibility (75) based on piezoelectricity. Ceramic-based piezoelectric devices generate much higher voltage than polymer-based devices. (76). But ceramic materials are not suitable for fabric application because ceramic-based piezo-electrics are fragile compared to their polymer-based counterparts. Advantages of polymer-based sensors over ceramic-based sensors include greater flexibility, lighter weight, and higher conformity (77). In addition, thanks to the high ease of processing and versatility of piezoelectric polymers, it is possible to provide ease of production by methods such as electro-spinning (78) and 3D printing (79). Wearable devices can interact closely with different parts of the human body, such as the ankle, neck, wrist, knee, and foot (80), or clothes can be made from rope obtained from this smart material (81). It is used as a wearable system designed to examine various medical parameters. E.g.: For the monitoring of the vital functions (heart, breathing, body temperature, blood oxygen level, activity, and movements) of the emergency personnel, for the monitoring of the breathing rhythm, in the follow-up of stroke rehabilitation and cardiovascular diseases (82).

There are studies on the measurement of vital signals with the help of piezoelectric sensors (83). These systems, called triboelectric nano-generators (TENG), are systems that will inevitably encourage the rapid development and widespread applications of the next-generation wearable electronics and versatile artificial intelligence systems, with the integration of advanced nano-generator technology with traditional textile processes. TENGs provide intelligent textiles with multifunctional self-sensing capabilities by collecting mechanical energy, while textile products are made wearable with their versatile flexible designs. However, there are still difficulties in preparing TENGs and finding a field of application. It is so difficult to obtain fiber/fabric-based TENGs with outstanding textile performance as well as product acquisition with excellent electrical output characteristics. Polyvinylidene fluoride (PVDF) and polylactic acid (PLA) polymers and co-polymers are the most studied in the literature (84). There is a need for both more practical research and expert personnel in this area.

Table 2. Current studies on smart clothing.

PREPARED METHOD	PIEZOELECTRIC POLYMERS	ELECTRODE	APPLIED FORCE/ OUTPUT VOLTAGE	SENSITIVITY	PRODUCT	REF.
Electrospinning	PVDF-5 wt % MOF nanofiber composite	Cu	arterial pressure (4.8 N) /568 (mV) (At normal body condition)	0.118 V/N	monitoring radial pulse	(85)
Embroidery yarn	poly-l-lactic acid (PLLA) fibers		Load applied to the fabric, 1 mN -10 N		motion tracking	(81)
Vertically aligned, micropillars	P(VDF-TrFE) film	One pair of cross electrode arrays	0.5-10 N/ 2.516 V	228.2 mV/N	dynamic tactile sensing	(86)
Electrospinning	polyvinylidene fluoride/Ag nanowire nanofibrous membrane (NFM)+ethyl cellulose NFM	two layers of breathable and comfortable conductive fabrics	3×10^{5}-6 $\times10^{6}$ V	1.67-0.20 V kPa^{-1}	motion detection and heart rate monitoring (Pressure sensitive)	(87)
Films	double-layer polyvinylidene fluoride (PVDF)	silver nanoparticle ink electrodes	output ultrasonic wave (2-30 Hz)		wearable ultrasonic sensor for Ultrasound Measurement of Skeletal Muscle Contractile Parameters	(88)
Electrospinning	polyvinylidene fluoride (PVDF)/boron nitride nanosheets (BNNSs) composite nanofibers	Al	4V-16V	PVDF1.5BN= 0.025 V kPa^{-1}	Wearable pressure sensor for medical applications	(89)
Electrospinning	PVDF based nanocomposites loaded with $BaTiO_3$ nanoparticles (NPs)	copper foils electrodes	max. 50 V	tensile strength (26.7 MPa)	• Distinctive piezoelectric signals observed for	(90)

					different motion styles. Wearable electronics and voice reorganization fields.	
Melt spinning	Molten poly (L-lactic acid) (PLLA)/$BaTiO_3$	with silver paste, and Cu	constant force of 2.9 N at 9 s^{-1}		Wearable textiles for use in the medical field	(91)
Coaxial electrospinning	**Inner Core** / **Outer Shell**: **PVDFHFP** / PVDF-ZnO; **PVDFHFP** / PVDF-TiO_2; **PVDFHFP-TiO_2** / PVDF-ZnO		Max. 14V	Five higher dielectric constants	• Detects human movements in various frequencies • Wearable pressure sensor	(92)
Electrospinning	polyvinylene fluoride (PVDF)/LiCl	Two copper strips by silver paste were set on both sides of the aluminum foils	3 V and 0.5 μA with a power density output of 0.3 μWcm^{-2} at the frequency of 200 Hz.	100 Pa %0.16 °C	Self-generating energy, wearable and implantable	(93)
Electrospinning	P(VDF-TrFE) nanofibers	Two 3D-printed frames with copper stripes as electrodes into a drum-like structure	Electrical signals up to 17 mV in response to low frequency between 100-400 Hz		• preserves electro-acoustic responses • in vitro cochlea models	(94)
Electrospinning	Nylon-11		α-phase fibers=3 mV δ′-phase fiber=12 mV	α-phase fibers=0.02 $mVkP^{-1}$ δ′-phase fiber=0.13 $mVkP^{-1}$	Wearable pressure sensor for medical applications	(95)

3.2. Drug Release

Piezoelectric polymers are used in the form of artificially engineered nano-robotic systems to control the targeted release of the drug. The purpose of this system is to control the speed at which the drug is released and where it is released. Nano-robotic systems are systems that release drugs with precise movements guided by parameters such as high specificity pH and temperature (96-98). In Table 3, drug release systems made with synthetic piezoelectric polymers in the last year have been compiled This system also has some problems that need to be solved. These are the control of movement and on-demand drug release, prevention of off-target drug release in response to changes, measures encountered with cells and body fluids.

Table 3. Current studies on drug release.

PREPARED METHOD	PIEZOELEKTRIC POLYMERS	PURPOSE	RESULTS	REF.
electrospinning	DSF-loaded electrospun PVDF nanofibers	Developing a scaffold loaded with disulfiram to examine its effect on cancer	DSF-PVDF fibers exhibited anticancer activity	(99)
a nonsolvent induced phase separation (NIPS) process	ZNG-g-PVDF Membrane	The PAA-g-PVDF membrane is functionalized with zwitterionic nanohydrogels for a highly sensitive membrane that can be used in drug release.	the membrane with an ultrasensitive responsiveness to salt	(100)
spray coating (film) and electrospinning (non-woven)	Paclitaxel-VEGF loaded poli (L-lactic) (PLLA)	dual drug delivery system for cardiac treatment	Both films and nonwovens have significantly increased in vitro cell viability for human umbilical vein endothelial cells (EA.hy 926) with dual loaded PTX and VEGF.	(101)
ring-opening polymerization	Nisin-loaded in PLLA-g-CS nanogels/human dermis fibroblast cells	dual sensitive nanogel controlled release of antimicrobial drug	no toxic effect, used for infection therapeutic applications.	(102)
biodegradable polyester P(3HB-co-4HB) obtained in-house from *Cupriavidus malaysiensis*-- emulsion/solvent evaporation method	DCX-loaded nanoparticles P(3HB-co-4HB)	To encapsulate Docetaxel, which is poorly soluble in water, into nanoparticles without affecting its physicochemical properties and to examine its anticancer activity.	P(3HB-co-70%4HB) nanoparticles-controlled drug release.	(55)
emulsion method	AZA-loaded PHBVHHx nanocarrier	Developing a nanta carrier system to reduce the bad solubility, short circulation time and side effects of AZA.	Medication reduced side effects in the treatment of systemic lupus erythematosus (SLE).	(103)

3.3. Tissue Engineering And Regenerative Medicine

Tissue engineering is a discipline that generally draws its strength from scaffold studies to support cell differentiation and growth. The new paradigm in tissue engineering is the need for active or intelligent scaffolding for the most accurate regeneration of specific tissues. Since electrical and electromechanical stimuli provide the most suitable environment for the determination of tissue functionality in tissues such as muscle and bone, especially piezoelectric polymers are increasing their popularity day by day as a very necessary material during tissue regeneration (72). Piezoelectric polymers are widely used in tissue engineering; PVDF, P(VDF-TrFE), PHBV, Polyamides, and PLLA. Piezoelectric polymers improve cell behaviors such as attachment, migration, proliferation, and differentiation. Not only cells but also extracellular matrix proteins such as collagen, fibrin, and keratin are known as piezoelectric and can generate electrical currents by mechanical stress. They enable many signaling pathways in the cell to be activated by electrical and mechanical stimuli (14, 104). Scaffolds made of piezoelectric polymers promote tissue regeneration in response to mechanical stimulation (104). The bioactive charged surface of scaffolds prepared from these materials can provide

enhanced cell adhesion and proliferation (105). In this section, we will summarize only the last year's status of piezoelectric synthetic polymer in tissue engineering in Table 4.

Table 4. Current studies on tissues and organs.

TISSUE ENGINEERING APPLICATION	PIEZOELEKTRIC POLYMERS	PREPARED METHOD	PURPOSE	RESULTS	REF.
BONE	PVDF/Col/PRP	electrospinning	Considering the high efficiency of tissue engineering in repairing bone defects the combined effect of collagen PVDF / col in combination with PRP on the osteogenic differentiation potential of human induced pluripotent stem cells (iPSCs).	• Osteogenic differentiation potential increased. • several growth factors, increased scaffold biocompatibility and its support for adhesion, growth, and proliferation of the stem cells raised.	(104)
	β phase - PVDF/GO composite scaffolds	selective laser sintering	Graphene oxide (GO) was introduced into PVDF scaffold manufactured via selective laser sintering, aiming to enhance piezoelectric effect of PVDF by increasing β phase content.	Demonstrated that the PVDF/0.3GO scaffold with improved β phase exhibited the maximal output voltage (~8.2 V) and current (~101.6 nA), which were improved by 82.2% and 68.2%, respectively, in comparison with pure PVDF.	(83)
	PLLA nanofiber membrane and sensor	electrospinning / nanofiber	By combining Electrical stimulation with tissue-engineering approaches (which rely on biomaterial scaffolds to construct artificial tissues), a replacement bone-graft with strong regenerative properties can be achieved while avoiding the use of potentially toxic levels of growth factors.	The PLLA nanofibers offer an ECM (extracellular matrix) like environment which not only promotes cell growth/differentiation but also generates direct electrical-stimulation under remotely-applied acoustic wave.	(106)
	• GO/PLLA • rGO/PLLA	electrospun hybrid scaffolds	dielectric graphene oxide (GO) and reduced graphene oxide (rGO) nanofillers use to cure piezoelectric properties of PLLA.	the increase of GO/rGO content resulted in the formation of thinner fibers.	(107)
	PHB- Keratin	electrospun scaffolds	PHB and keratin using electrospinning technique for the effects of different quantities of keratin on structural, mechanical, and biological properties of PHB scaffold were evaluated in vitro environments.	• a highly porous structure (higher than 80%) • the of cells adhesion, viability, proliferation, ALP secretion became better. • According to the mechanical	(108)

				properties, the addition of keratin up to 10 wt. % increased the tensile strength and toughness of electrospun scaffolds. • the degradation of PHB is increased in the presence of keratin.	
	aloe vera–derived gel-blended poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) nanofibrous scaffold	electrospinning	Composite scaffolds fabricated by natural and synthetic polymers in the field of tissue engineering, and given their combined properties that can play a very useful role in repairing damaged tissues.	aloe vera gel in the scaffold; • increased its osteoinductivity, • increased the scaffold biocompatibility, • increased the amount of cells attachment to the scaffold, • increased the growth and proliferation of the stem cells.	(109)
	poly (3-hydroxybutyrate) PHB-Chitosan (Cs)/ multi-walled carbon nanotubes (MWCNTs) nanocomposite coating deposited on nano-bioglass (nBG)-titania ($nTiO_2$) scaffolds	fabricated by foam replication method	using the nanocomposite coatings on bioceramic scaffolds to improve the properties of these scaffolds.	• porosity above 75% PHB-Cs/ MWCNTs coated scaffolds. • a significant effect on bioactivity and cellular behavior. • the of cells adhesion, viability, proliferation, ALP secretion became better.	(110)
	PVFT-BGM nanofibrous scaffolds	electrospinning	The multilaterally biomimetic bioactive piezoelectric nanofibrous scaffolds for synergistically enhancing the periosteum formation and critical-sized bone regeneration.	• proliferation, migration and osteogenic differentiation of mBMSCs. • Supports in vivo formation of periosteum-like tissue and critical size bone regeneration. • the negative pole of PVFT gather positive Ca^{2+} from BGM and activate the CaSR of osteoblasts and further promote osteogenesis.	(111)
	PVDF/nano-hydroxyapatite (nHAp) nanofibrous scaffolds	electrospinning	scaffold production that mimics extracellular matrix with bioactive and bactericidal properties in order to provide adequate conditions for regeneration of damaged bone	• the highest cell viability, total protein, and alkaline phosphatase activity. • 99.8% efficiency against *Pseudomonas aeruginosa* bacteria.	(112)
NEURAL	PVDF/BT/MWCNTs	electrospun scaffolds	to assess the use of both electrical and topological cues in piezoelectric	• Predict nerve differentiation and nerve regeneration	(113)

			scaffolds for nerve regeneration.	through topographic or electrical stimulation	
	PVDF/PCL	a simple cast/annealing-solvent displacement method	Use of Piezoelectric materials for bioelectric therapies in nerve tissue engineering	• stimulate cell proliferation and differentiation. • electrophysiological, morphological and functional nerve restoration.	(114)
INNER EAR	P(VDF-TrFE)/$LiNbO_3$	electrospinning	use of piezoelectric polymers to mimic the function of the cochlear sensory epithelium and to stimulate auditory neurons (as an alternative to CI)	• had a strong immunomodulatory activity, • direct antibacterial activity against *P. aeruginosa* • enhanced HBD-2 in HaCaT epithelial cells • showed an enhanced piezoelectric response 90 ± 2 mV • promotes human nerve-like cell growth in vitro.	(115)
SKELETAL MUSCLE	PVDF films	films	Skeletal muscle is not piezoelectric tissue like bone, but critically needs an electromechanical stimulus to support tissue growth and development.	• Surface charge and negative polarization promote C2C12 myoblast cell elongation and improve adhesion of the cell to the scaffold. • in addition, the energy required for the separation of dead cells is higher in 3D cell culture developed with negatively charged scaffolds.	(116)
TENDON	PVDF-TrFE	a two-step near-field electrospinning	bioelectronic therapies of musculoskeletal disease for accelerating functional recovery through the activation of tissue regeneration signaling pathways.	• Body motion powered electromechanical stimulation can control • the expression of TRPA1 and PIEZO2 receptors • stimulate tendon-specific tissue repair processes.	(117)
SILK	the self-adhesive matrix of PDA-PAAm hydrogel and the TENG based on aligned PVDF nanofibers mat	Electrospinning prepared PVDF nanofibers mat	use of TENG to give electrical stimulation to the wound area	• Accelerate skin wound healing. • skin growth by mimic, • accelerates the cell proliferation and migration, • enhances the expressions of regeneration related	(118)

				proteins such as CD31, VEGFA, and TGF-β1 at the wound site, • allowing collagen deposition, new blood vessel formation, re-epithelialization, and even partial hair follicle regeneration, • allowing for the quick and better repair of the wounds.	
LUNGS	ZnO/P(VDF-TrFE)	electrospun fiber meshes	Due to the morbidity and lethality of pulmonary diseases, new biomaterials and scaffolds for to support the regeneration of lung tissues, while ideally providing protective effects against inflammation and microbial aggression.	• Includes sufficient cytocompatibility, • tunable mechanical properties, • good piezoelectricity, strong immunomodulatory properties, • good antimicrobial function	(119)

4. CONCLUSION

In this review, we have examined various applications for smart synthetic piezoelectric polymers in smart clothing, drug delivery systems, and tissue engineering in the last year and seen the use of a wide variety of copolymers used in sensors, health monitoring, tissue/organ treatments, and drug delivery systems. It can be clearly seen that synthetic piezoelectric polymers constitute extremely modern material approaches also in these studies. With these materials, effective applications and excellent perspectives can be presented in many medical devices. We hope to shed light on future development opportunities by emphasizing the importance of synthetic piezoelectric polymers in the medical field.

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