

Electrospun polymers for controlled release of drugs, vaccine delivery, and system-on-fibers

A. VASEASHTA*, I. STAMATIN^a

Nanomaterials Processing & Characterization Laboratories, Department of Physics & Graduate, Program in Physical Sciences Marshall University, Huntington, WV 25575-2570, USA

^aNanosciences & Alternative Energy Sources Research Center, University of Bucharest, Faculty of Physics, Romania, Bucharest- Magurele, MG-38, Romania

This investigation presents a comprehensive overview of our ongoing efforts and future directions of research using inorganic and organic nano-biomaterials. One of the key objectives of our research is to develop sensors that can readily detect gases, and chemical and biological molecules for applications ranging from contamination to environmental pollution. Among several processes used to fabricate chem.-bio sensors, we are currently using an electrospinning process to develop several composite fibers with application in chemical, biological, and gas sensing application. As an extension, we have investigated several biodegradable polymers for possible construction of excipient therapeutic templates. There are a number of natural and synthetic biodegradable polymers that are being used and proposed for targeted vaccine and drug delivery, and for both soft and hard tissue repair. Such fibers-by-design address many issues relating to the fundamental challenge in the synthesis of fibers for System-on-Fiber (SOF), and will have tremendous application in network appliances, personal entertainment, and global security and defense.

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1. Introduction

Scientific study of nanoscale materials and systems is a promising discipline, as it refers to the fundamental understanding and technological advances arising from the exploration of certain unique physical, chemical, and biological properties that are attributable to their small size (surface area and size distribution), surface structure (surface groups, modification using functionalization), physical characteristics (luminescence, quantum dots, electronic characteristics), and chemical composition (crystallinity, purity, solubility)[1]. Advances in synthesis and characterization methods have provided the means to study, understand, control, or even manipulate the transitional characteristics between isolated atoms and molecules, and bulk materials. Recently, various nanoscale materials with new architectures, improved functionality, and remarkable properties have been developed with several applications in chemical and biological sensors, nanobiotechnology, nanophotonics, and in-vivo analysis of cellular processes.

Global threats such as escalation in terrorist activity have generated tremendous demands for innovative tools capable of detecting major explosives and chemical warfare agents (CWAs) in a faster, simpler and more reliable manner at the site of event. Rapid identification of most explosives and CWA(s) will allow first responders and emergency personnel to make important decisions concerning barricading, evacuating, or efficient decontamination of a particular site and will prevent responders from becoming victims themselves. Furthermore, with ever increasing potential and risk for

inadvertent or deliberate contamination of the environment, food and agricultural products due to terrorism or even naturally occurring threats such as avian bird flu; decentralized sensing has become an important issue for several federal agencies. In clinical medicine, many decentralized laboratory facilities conduct routine clinical trials employing direct reading, portable, lab-on-chip kind systems.

Our initial investigation [2] indicates that a nanotechnology based sensor platform will enable the direct electrical detection of biological and chemical agents in a label-free, highly multiplexed format over a broad dynamic range. This platform utilizes functionalized nanoparticles, nanotubes and nanowires to detect molecular binding with high sensitivity and selectivity. Nanotechnology based platforms can detect a broad range of molecules, viz., DNA, RNA, proteins, ions, small molecules, cells and even the pH values. Simultaneous detection in liquid and gas phases facilitate multiplexable parallel detection of multiple agents. Progress in the application of nanostructured materials for chemical and biological sensing will significantly impact efficient data collection, processing, and recognition with minimum false positive counts. The ability to monitor chemical and biological agents at the originating source by such sensor systems offers significant advantages in terms of providing a timely warning and an ability to process a smaller sample size than the current technologies allow.

In earlier investigations [3-4], it was observed that the nucleic acid layers combined with nanomaterials based electrochemical transducers produce a new kind of affinity biosensors as "DNA Biosensor" or "Genosensor"

for small molecular weight molecules. Genosensors are attractive devices for converting the hybridization event into an analytical signal for obtaining sequence-specific information in connection with clinical, environmental or forensic investigations. The development of novel and sensitive assays for DNA hybridization and detection is an increasingly important research field. Researchers hope that continued development through combined efforts in microelectronics, surface/interface chemistry, molecular biology, and analytical chemistry will lead to the establishment of genosensor technology as a major component of analytical biochemistry. The design and fabrication of DNA-modified surfaces and materials which are reproducible, stable and selective to complementary DNA sequences are crucial in the development of emerging analytical tools such as DNA chips or even simple diagnostic devices for detecting DNA sequences. These devices are used for fast, cost-effective and diagnosis of inherited or infectious diseases, and early determination of infectious agents in various environments.

2. Nanomaterials for sensors and detectors

Developments in the human genome project (HGP) have furthered knowledge in the molecular basis of diseases influenced by external pathogens and internally from variations within the human genome, resulting in a plethora of new molecular therapeutic targets for drug design and discovery. Traditional methods for DNA sequencing, based on the coupling of electrophoretic separations and radioisotopic (^{32}P) detection, are labor intensive and time consuming thus unsuitable for routine and rapid medical analysis, particularly for point-of-care tasks. Advances in bio-sensors based on nucleic acid have led to the development of genosensor technology for gene sequence analysis and for nucleic-acid ligand binding studies [5-11]. The knowledge obtained from emerging electrochemical DNA biosensors (genosensors) will advance biomedical and environmental research as evidenced by recent electrochemical monitoring of DNA hybridization [12-22]. Direct electrochemical DNA analysis based on guanine signal has been reported in the literature [12,13] with expected applications for producing electrochemical microchips for portable, hand-held medical diagnostic devices. Because genosensors are compatible with existing micro and nanofabrication technologies, they enable design of low-cost, devices that aid in the detection and diagnosis of inherited diseases [14,15,18]. Combined efforts between microelectronics, molecular biology, surface/interface and analytical chemistry researchers will facilitate establishment of genosensor technology as a major component of analytical biochemistry. Immediate applications include direct quantification of DNA samples for use in sequencing or polymerase chain reactions (PCR), and pharmaceutical testing and quality control. They offer clinical potential for detecting pathogenic bacteria, tumors, genetic disease, and forensics via credit card-sized sensor arrays [23,24].

2.1. Experimental methodologies: sensors and detectors

Vital aspects of electrochemical biosensors development are sensing strategies maintaining critical dynamics of target capture and generation of a sufficient recognition signal. These devices can be used for monitoring sequence-specific hybridization events directly, based on the oxidation signal of guanine, DNA intercalators (metal coordination complexes, antibiotics etc.), or using some metal tags viz. gold or silver nanoparticles or magnetic particles, for detecting the oxidation signal of gold or silver, or electro active DNA bases in the presence of DNA hybridization.

Yet another type of biosensors is developed by using surface plasmon resonance (SPR) to detect *E-coli* O157:H7 bacteria. Self assembled monolayers (SAM) layer of thiols were activated by passing an equal mixture of freshly prepared 0.4 M *N*-ethyl-*N'*-(dimethyl-amino dimethyl-aminopropyl) carbodiimide hydrochloride (EDC) and 0.1 *N*-hydroxy-succinimide (NHS), to produce receptors (NHS esters) capable of binding to the amino group of antibodies to form an amide bond. An antiserum against *E. coli* O157:H7 was suspended in sodium acetate (NaOAc) (pH 5.5) or Phosphate Buffered Saline/Tween (PBST) (pH 7.4), and transferred over the activated surface. Reversibly bound antibodies were cleaned from the surface by flowing ethanolamine (pH 8.5). The sample was returned to PBST (pH 7.4) to remove unbound antibodies from the surface, thus establishing a baseline for the sensorgram. Also, the porous silicon (PS) biosensors were developed using bulk silicon crystal, by partial electrochemical dissolution in hydrofluoric acid solutions. Depending upon the etching conditions, PS has a very complex, anisotropic, and nanocrystalline architecture of high surface area. The PS surface is hydrophobic, and functionalization of the surface renders it as a biomaterial. The PS biocompatibility can be improved by a suitable change of the surface parameters. It is determined by two main properties: the normal electrochemical potential and the surface energy with respect to the living body. Studies of the electrochemical potential of a number of materials used in medicine have shown that only carbon, gold, and platinum have values close to those of living tissue: +0.330, +0.332, and +0.334 mV respectively. The surface energy of these elements ranges from 20 to 30 erg/cm², which likewise corresponds to the values for living tissue. Generally, the carbon layer structure is formed by mixing sp² and sp³ bonding. A high fraction of sp³ bonds gives a highly hydrophobic surface, which is responsible for the cell attachment. For biological applications, we have developed technology to obtain different PS layers with 35-50% porosity on Si-p+ (100) and (111), followed by different treatments for surface structure modification/ stabilization, by which the surface acquires biomaterial properties.

Finally, the CNTs and nanowires, grown using thermal CVD using C₂H₆ in different ambient environments on Ni and Fe coated Si substrates, were also used for biosensor applications. CNTs are particularly biocompatible and offer excellent conductivity. These characteristics, in conjunction

with reliable and reversible response to bio-chemical agents allow bio-probing and detection applications. Furthermore, a possible interfacing of CNTs with electro active proteins, by establishing molecular links provides a convenient

vehicle for studying cell organization. Fig. 1 (a)-(c) shows detection of chemical/ biological agents using electrochemical sensors, SPR and AFM, respectively.

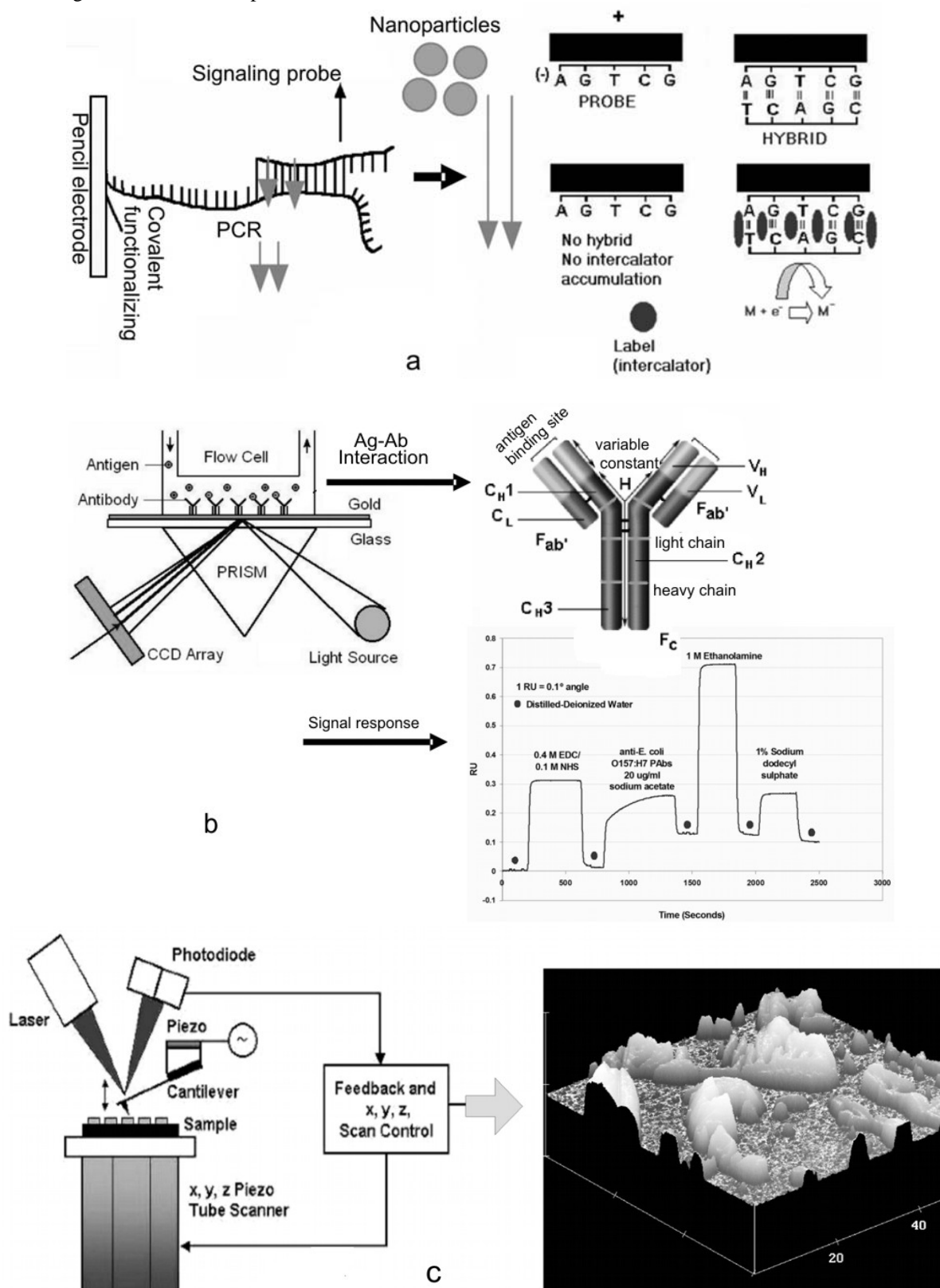


Fig. 1. Detection of chemical/biological agents using (a): Electrochemical sensors, and hybridization sensing strategies, (b): SPR and a typical response of a flow cell and, (c): AFM on E-coli, bound to its corresponding antibody on a SAM based gold chip[2].

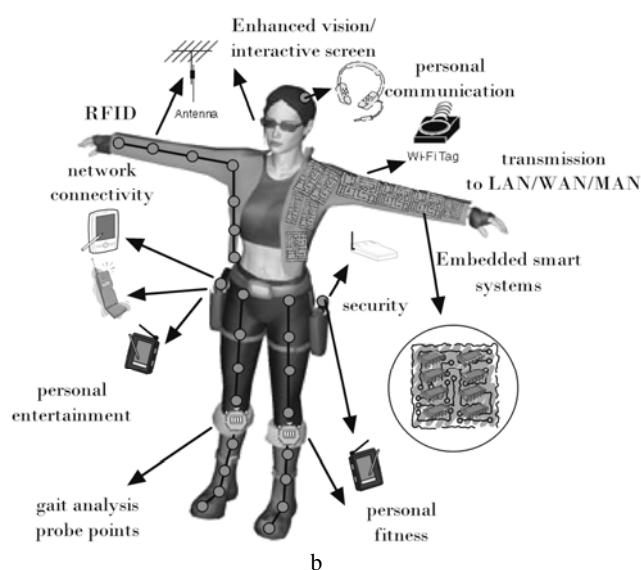
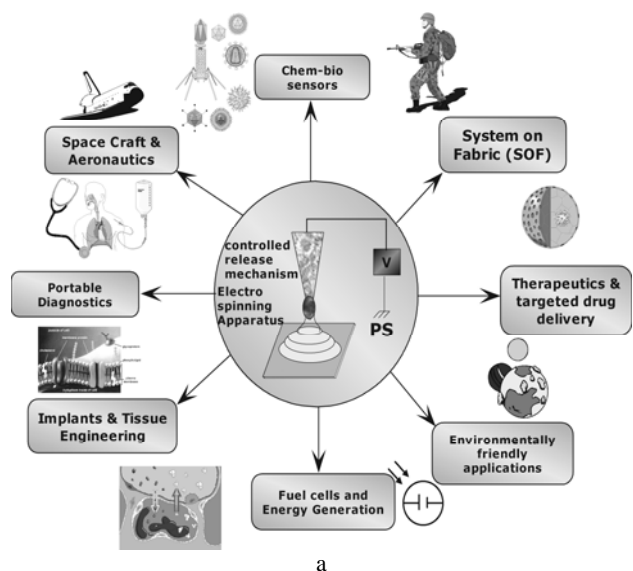
4. Electrospinning of polymers and composites

The process of electrospinning for preparing fibers provides a unique possibility to produce fibers of varying porosity and thus high surface area. The high surface area/volume ratio combined with its potential biocompatibility and biodegradable nature offers tremendous promise for diverse biomedical applications from tissue engineering, targeted vaccine delivery, and non-thrombogenic materials for blood contacting applications. Biodegradable polymers are highly desirable for long-term drug delivery applications because they degrade in the body to biologically inert and compatible molecules. By incorporating a drug into biodegradable polymers, dosage forms of various shapes and sizes can release the drug over prolonged periods of time. Secondary surgical procedures common after the completion of dosing regimens are not needed as the remaining polymer dosage naturally degrades. Thus, biodegradable polymers offer a novel approach for developing simple and convenient sustained release drug delivery systems [25]. Many biodegradable polymer chemistries have been proposed for these applications; however, the most common and successful are polyesters first investigated as degradable sutures. These polymers include poly(glycolide), poly(D,L-lactide), and their related copolymers poly(D,L-lactide-co-glycolide). Current commercial products based on these materials include Decapeptyl[®], Lupron Depot[®], and Sandostatin LAR[®]. Under suitable conditions, most synthetic and natural polymers demonstrate electrospinning; thus allowing nanofiber preparation from nanoparticles or vaccine-impregnated polymers [26], fibers demonstrating electro-optical phenomena [27], and ceramic precursors [28].

4.1. System on Fabrics (SoF): Smart Textiles

The advent of mobile and pervasive computing; wireless-networks; network appliances; flexible substrates; and e-textile are enabling the development of systems on textile or system on fibers (SoF). The ability to disperse ceramics, metal oxides, nanoparticles, and carbon nanotubes in polymers solutions and develop fibers thereafter employing electrospinning has produced new pathways for functional fibers, referred here as SoF – that have electronics and interconnections woven into them. Such systems demonstrate tremendous potential towards the development of portable functional devices such as functional fibers embedded with data communications systems, medical and health monitoring, personal fitness, defense systems, mobile computing, targeted and time-released delivery of vaccines, protective armor, chemical-biological sensors, Radio Frequency Identification device (RFID), Global Positioning System (GPS), and interactive geographical information systems (GIS). The technology offers feasibility for the development of systems with physical flexibility and size unachievable with current and

conventional manufacturing technology. Recent advances in textiles have led to the investigations in electronic textiles for wearable computing systems and signal transmission [29,30]. The research area has gained significant momentum, however, the use of fibers using electrospinning of high performance polymers and polymer composites for smart textiles has been suggested here for the first time. The fabric consists of both conducting polymers and components woven into a pre selected and desirable pattern. The vision of SoF sketches a scenario that enables context-aware functionality, data communication interface, parallel detection of chem.-bio sensors, and provides for invaluable real-time information for soldiers in combat theatres to execute critical decisions in a timely manner. Figure 2(a) illustrates some of the targeted applications of our current programs and figures (b) and (c) conceptualize the architectural layers of SoF in wearable layers adopted for civilian and soldiers in combat theatres.



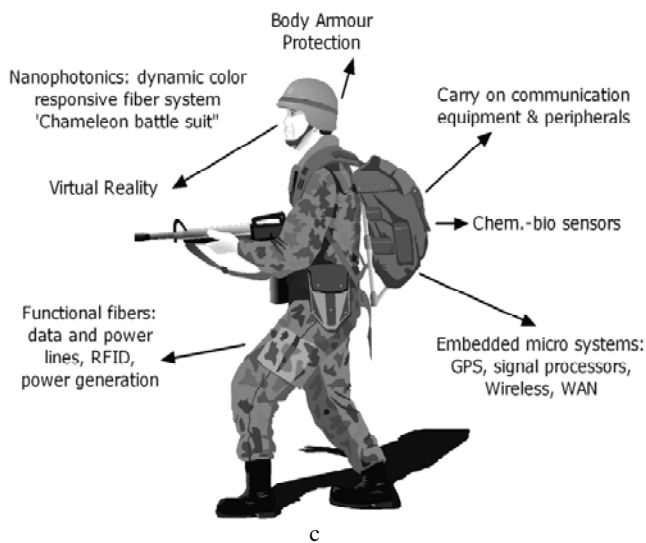


Fig. 2. (a) Targeted and potential applications of polymers/ceramics based electrospun fibers. (b-c) conceptualization of the architectural layers of SoF in wearable layers, adopted for civilian and soldiers in combat theatres.

4.2. Experimental methodologies: electro-spun polymer and composite fibers

Several synthetic and natural polymers, polymer composites, polymers impregnated with nanoparticles, carbon nanotubes, and compounds for mechanical, electrical, and biological applications were attempted

using single and double jet electrospinning apparatus. A typical electrospinning apparatus consists of a microprocessor-controlled syringe pump with high metering precision at low, pulse-free preset rate and volume control. The internal diameter of the syringe is used by the control program to calibrate the pump and deliver a pre-determined volume and flow rate. The electric field is applied with a high voltage (30 kV) power supply by connecting the metal discharge needle and a ground stationary or rotating electrode. The strong electric field on a polymer fluid generates an electrostatic force on the surface against the viscous stresses of the polymeric mass, thus producing jets towards the other electrode. A Taylor cone is [31] generated in the jet when a hydraulic effect produced by the syringe plunger to the polymer solution is modified by the strong electrostatic field. The shape of the cone, employing parameters such as viscosity; conservation of mass, charge, and momentum; electric field; surface tension; air drag; and Coulombic and Gravitational forces has been modeled by several investigators. In our experiments, we have demonstrated controlled jet instability to produce two and three Taylor cones, with several possible applications [32]. Table 1 provides a list of polymers (synthetic, natural, and biodegradable), ceramics, electro-ceramics, and bio-ceramics that are currently under investigation, their composition, molecular weight, approximate range of loading, and intended applications. The work is currently in progress and only a representative work is reported here.

Table 1. A sample list of polymers (synthetic, natural, and biodegradable), ceramics, electro-ceramics, and bio-ceramics currently under investigation.

Polymers & Composites	Composition	Molecular weight	Loading	Applications/ Comments
Synthetic	Polystyrene/Dichloroethane	299,000	CNT	Field Emission
	Nylon (6,12)/1,1,1,3,3,3 Hexafluoro-2-propanol	-----	CNT	Flexible Substrates
	Poly(etherimide)/1,1,2-Trichloroethane	30,000	CNT	Mechanical Strength - SoF
	Polyacrylonitrile (PAN)/ Dimethylformamide (DMF) (also dimethyl acetamide (DMAc))	114,000 M vol.	CNT ZnO	Strength Sensors (SoF)
	Polymethylmethacrylate (PMMA) in acetone, chloroform, Toluene	540,000	None	Porous fibers
	Polyvinylpyrrolidone/Ethanol/DMF	58K-1.3M	Bi ₂ S ₃	CT imaging
	Polypropylene in Acetonitrile (ACN), and dichloromethane (DCM)	-----	TEA BF ₄	Conducting Polymers -SoF
	Polyurethane/DMF Polycarbonate/DMF	42,000	CNT	Protective Clothing
Natural	Lecithin/Dimethylformamide	-----	None	Biomembranes
	Lecithin/Dimethylformamide	-----	Bi ₂ S ₃	CT imaging
Biodegradable	Poly (ε-caprolactone) (PCL)	-----	PLA/PGA	Wound dressing

Polymers & Composites	Composition	Molecular weight	Loading	Applications/ Comments
	Poly (L-lactide/co ϵ -caprolactone) (PLLA/CL)	150,000	PLA/PGA Collagen	Stents Tissue/Scaffold
	Poly (ethylene oxide)/water	400,000	PCL	Hollow Fibers
	Polyglycolide		PCL	
	Poly (ethylene oxide)/water	400,000	MoO ₃ , ZnO, TiO ₂	Sensors
	Poly (L-lactide/co ϵ -caprolactone) (PLLA/CL)	150,000	Bi ₂ S ₃ Collagen	CT imaging
	Poly (L-lactide/co ϵ -caprolactone) (PLLA/CL)	150,000	Metal nanoparticles	Targeted drug Delivery
Ceramers	Polyacrylonitrile (PAN)/ Dimethylformamide (DMF)	150,000 M vol.	TiO ₂	Conductive & PV Polymer
	Polydiphenoxyphosphazene PDPP		SiO ₂ (Y, Er)	Glass/ceramic
Electro-optic polymers	Poly(acrylic acid)-polypyrrene methanol (PAA-PM)/ Dimethylformamide	50,000		Optical sensors
	Poly (vinyl acetate)/Acetone		GeO ₂	1D Opto- electronics
Bio-ceramers	Poly(l-lactic) acid, poly(glycolic) acid, Poly(l-lactide/glycolide)	70K/>150K /10-20K	Collagen Mefoxin	Bone repair Antibiotics

5. Results, discussion, and future directions

Prospective use of biodegradable polymeric systems for controlled drug delivery as an alternate and efficient route for vaccine administration, orthopedic materials, semi-permeable membranes, peripheral nerve regeneration, and tissue engineering is a topic of significant research. Some materials that are currently being used or studied for controlled drug delivery include, poly(2-hydroxy ethyl methacrylate), poly(N-vinyl pyrrolidone), poly(methyl methacrylate), poly(vinyl alcohol), poly(acrylic acid), polyacrylamide, poly(ethylene-co-vinyl acetate), poly(ethylene glycol), and poly(methacrylic acid). More recently, the time-controlled release characteristics of certain polymers including polylactides, polyglycolides, poly(lactide-co-glycolides), polyanhydrides, and polyorthoesters are specifically being investigated for medical applications. A general criterion for selecting a polymer for use as a degradable biomaterial is to match the mechanical properties and the degradation rate to specific parameters. The greatest advantage of biodegradable polymers is that they are broken down into biologically acceptable, metabolized and removable molecules. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment. These degradation products - desirable and potentially non-desirable - must be tested thoroughly. Some of the factors affecting biodegradation of polymers are presence of ionic groups, low-molecular-weight compounds, and unexpected units or chain defects, configuration structure, molecular weight and its distribution, morphology, functionalization process, implantation site, adsorbed and absorbed compounds (water, lipids, ions, etc.), physicochemical factors (ion exchange, ionic strength, pH), and physical factors. Much of the development of novel materials in controlled drug delivery focuses on

preparation and use of these responsive polymers with specifically designed macroscopic and microscopic structural and chemical features[33]. Such systems include copolymers with desirable hydrophilic/ hydrophobic interactions, block copolymers, networks responding via hydrogen or ionic bonding, dendrimers or star polymers as nanoparticles for immobilization of enzymes, drugs, peptides, or other biological agents, biodegradable polymers, and new blends of hydrocolloids and carbohydrate-based polymers. These new biomaterials with desirable functional groups are being created by researchers who envision their use not only for innovative drug delivery systems but also as potential linings for artificial organs, as substrates for cell growth or chemical reactors, as agents in drug targeting and immunology testing, as biomedical adhesives and bioseparation membranes, and as substances able to mimic biological systems. Some of the most promising medical applications include treatment of primary pulmonary hypertension (PPH) and pulmonary arterial hypertension (PAH) by time-controlled release templates impregnated with anticoagulants and calcium channel blockers, bioscaffold that mimic extracellular matrix (ECM) topology [34], polyesters combined with phosphatidyl choline for biomimetic applications [35], intravascular stents from a blend of polyactide and trimethylene carbonate [36], dystrophin gene immobilized templates for curing aging skeletal muscles [37], cellulose based scaffold for cartilage tissue engineering [38], and esophageal tissue engineering [39]. We propose that employing controlled jet instability to produce multiple Taylor cones may allow fabrication of fibrous scaffold for blood vessel engineering [33].

In yet another aspect of our investigation, synthetic and regenerated polymers are studied for possible use in functional textiles and apparel. Composites of high performance polymers with metal oxides, glasses coated with rare earth metals, and biocompatible compounds are

prepared and studied for electrical conductivity, optical response, and chemical and biological detection. Carbon nanotubes (CNTs) have a wide range of unexplored potential applications ranging from aerospace, field emission, gas adsorbents, sensors, and composites warranting major research efforts. We have investigated several polymers loaded with varying concentrations with carbon nanotubes (CNTs). Since CNTs have excellent field emission properties offering applications ranging from display panels to portable x-ray generation devices [40], we have studied several loading of CNTs in the matrix of PS, PEO, PEI, PAN, and PU. The effect of CNT contents on electrical and rheological properties are currently under investigation. The ability to develop polymer composites, ceramers, electro-ceramers, and bio-ceramers with varying characteristics and biocompatibility offers tremendous potential to develop fibers with desired shapes and characteristics, resulting in many hybrid components. The functional components form integral parts of many functional wearable fibers leading to a SoF.

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*Corresponding author: prof.vaseashta@marshall.edu