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Electrospun Nanofibers as 3D-Structures for Nanomedicine

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Abstract

The design and engineering of advanced nanostructures could allow for the development of novel medical tools useful for earlier diagnosis, more individualized treatment options, and better therapeutic strategies. Nanotechnology researchers are working on a number of different manufacturing techniques to combine organic and inorganic matrixes to biological molecules for regenerative medicine or delivery medication. In this frame, electrospinning is widely investigated to realize 3D fibrous organic, inorganic or composite nanostructures. Electrospun nanosized systems not only preserve and improve drug pharmacological activity, but also define new administration routes including transdermal delivery, permit to exclusively target the damaged site and mimic tissues structures and functionalities.

Keywords: Electrospinning; 3D nanostructures; Tissue engineering; Drug delivery

Introduction

The possibilities offered by nanotechnology permit to improve life quality and to contribute to the economic growth of society addressing some of the world's societal challenges such as safe energy, risk environment, food security, health and wellbeing. In the past few years, research activities in the nanotechnology field have been most plentiful to find applications ranging from medicine to space exploration. Thanks to nanotechnology, which according the definition adopted by the National Nanotechnology Initiative is the manipulation of matter with at least one dimension sized in the range 1-100 nanometers, it is possible to explore, exploit and control the never envisioned properties that materials have at the nanoscale. For example, working down at the nanoscale, surface area is larger than similar volumes of macro-scaled materials, thus more surface is available to interact with the surrounding environment. Organic, inorganic or biological materials can be assembled at extremely small scales by using nanomanufacturing techniques in different nanostructures such as tubes, rods, dendrimers, wires, rings, capsules, fibers. By combining functional materials and nanostructures, an extensive variety of modified properties can be obtained facilitating innovative applications.

With the aim to draw on the natural scale of biological phenomena thus producing precise solutions for disease prevention, diagnosis, and treatment, the application of nanotechnology in the medicine field is earning tremendous importance in this era. The "bottom-up" approach combined with innovative manufacturing techniques allow to realize customized and engineered nanostructures useful for precise diagnostic imaging, efficient drug delivery, theranostic - which integrates both therapeutic and diagnostic capabilities into one single nanoplatform - and as scaffolds for regenerative medicine.

Among the nanomanufacturing techniques used to realize complex nanostructures, electrospinning has attracted exponentially increasing interest in the design and fabrication of both nanovectors and scaffolds based on a fibrous structure thanks to its high versatility and simplicity [1]. Electrospinning relies on the application of high voltages to a polymer viscous fluid (solution or melt). The electric field causes the elongation and stretching of the polymer solution in the form of a jet travelling in the air towards a collector at a different electric potential. If the polymer has sufficient molecular entanglements, the jet does not break up into droplets due to Raleigh insta-

bilities but deposits continuously on the collector to create a non-woven mesh of fibers. The simplest setup process involves a single needle and produces monolithic fibers; the more advanced coaxial process - two coaxial needles fed with different solutions - can generate complex morphologies as core–shell fibers or tube [2]. Infact, as reported in literature, nanotubes can be prepared on the basis of polymer nanofibers which serve as sacrificial template (TUFT - TUbes by Fiber Templates) [3] **(Figure 1)**.

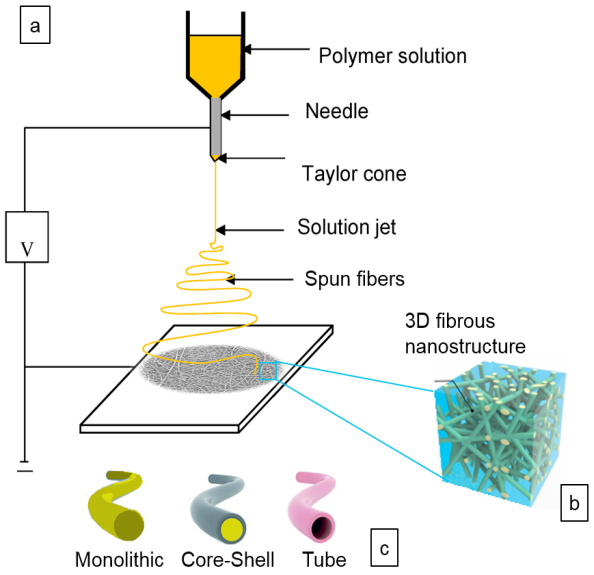

Figure 1: Schematic representation: (a) electrospinning basic setup, (b) 3D fibrous nanostructure and (c) different electrospun fibrous morphologies.

The electrospinning process is highly dominated by various factors depending on process parameters (voltage, feed rate, spinneret-collector distance, etc.), on intrinsic solution properties (polymer molecular weight, solvent volatility, solvent conductivity, etc.), and finally, on the presence of additives. By appropriately selecting solution and process parameters, electrospinning provides the opportunity for direct addition into electrospun nanofibers of a rich variety of substances: drugs (both hydrophobic and hydrophilic), biomacromolecules (such as proteins and DNA), nanoparticles and capsule, carbon nanotubes. In order to realize an efficient multicomponent fibrous system, it is necessary to verify the interaction between the different polymers and between the polymer and the filler.

The greatest advantages of electrospun 3D nanostructures are the high surface area of nanofibers as well as the three-dimensional open porous structure; both of them not only facilitate the interactions between the matrix and the surrounding biological environment but also reduce the constraint towards drug diffusion [4]. In addition, because of electrospun fibers have one dimension at the microscopic scale but another dimension at the macroscopic one, it is possible to combine the advantages possessed by nanostructures with the properties of conventional solid membranes, such as ease of manipulation and applicability in any size and shape. As result, non-woven textile are suitable for biomedical or healthcare applications both as implantable or non-implantable biomedical devices [5].

Now-a-days commercial usage of electrospun fibers across multiple applications has been exploited, the main applications regard above all filtering (Zeus Filtriq™, NnF MBRANE® – PUR) and scaffolding (Nanofiber Solutions™) and the realization of implantable structures in the body (AVflo™ Vascular Access Graft, NovaMesh™ Ventral Hernia Mesh).

In literature electrospun nanofibers have been broadly explored for providing targeted drug release, for providing sustained and stimuli responsive release profiles, for improving the dissolution rate of poorly water-soluble drugs, for wound healing, tissue engineering - both bone and neuronal tissues, and for encapsulating multiple functional components.

An electrospun fibrous system was investigated as designed device for efficient Artemisinin encapsulation and release. This system has been properly realized to preserve the pharmacological activity of drug by selecting a bilayer morphology: the core was a hyperbranched polymer acting as cage for the drug thus avoiding its crystallization; the shell was a hydrosoluble polymer able to facilitate drug dissolution in biological media. Results from biological invitro test revealed that the Artemisinin loaded into core-shell fibers has the potential to effectively inhibit proliferation of both P. falciparum parasites and prostate cancer cells [6].

Another study reports a simple and innovative method to form a 3D composite nanofiber implant, composed of PLGA-PLA-PCL nanofibers electrospun together, capable of releasing anti-glioma drug Temozolomide, continuously for one month into the brain tumor at a constant rate. Each fiber has a different release profile and results clearly indicated that prolonged drug release in the brain tumor is critical in inhibiting the recurrence of glioblastoma [7].

As concerning the use of nanofibrous structures as scaffold, Fasolino et al. reported the fabrication and application of eumelanin based nanostructures for neuronal tissue engineering. An appropriate procedure combining electrospinning, spin coating and solid-state polymerization process was established to realize the scaffolds that, successively, was used for neuroblastoma cell culture. Biological data showed that the scaffold was able to provide both mechanical support and biological signals thanks to its peculiar surface chemistry thus favoring cells growth and differentiation toward a more mature neuronal phenotype [8].

A variety of studies have been focused on the realization of composite nanofibrous structures combining many kinds of nanofillers (NFs) - metal, metal oxide, carbon, polymer, fluorescent NFs, and even biological molecules - with polymer fibers. For instance, novel structures can be engineered to mimic the crystal mineral structure of bones. Gönen et al. reported that strontium or copper doped bioactive glass particles have been successfully incorporated into gelatin/ poly(ε-caprolactone) (Gt/PCL) nanofibers through electrospinning process to realize scaffold. As the content of bioactive glass increases, they demonstrated that average diameter of the as-spun nanocomposite fiber mats also rises with further effects on the osteogenic, angiogenic, and antibacterial potential of the nanocomposite fiber mats [9]. An effective method was employed for preparation of scaffold based on polycaprolactone nanofibers using conducting polymer-functionalized reduced graphene oxide (rGO). The grafted rGO composites exhibited a good electroactivity behavior, mainly because of the enhanced electrochemical performance. The electrospun nanostructure underwent degradation about 7 wt% after 40 days, and was not able to induce cytotoxicity [10].

The work of Jin et al. reported for the first time the use of co-axial electrospinning to prepare theranostic systems with simultaneous encapsulation of therapeutic, diagnostic, and targeting agents in the form of core–shell fibers. Eudragit S100 was used to form the shell of the fibers, while the core comprised poly (ethylene oxide) loaded with the magnetic resonance contrast agent Gd(DTPA) (Gd(III) diethylenetriamine pentaacetate hydrate) and indomethacin as a model therapeutic agent. The use of the core/shell fiber delivery system permits both the indomethacin and Gd(DTPA) to be delivered simultaneously to the colon. This should permit theranostic studies to be undertaken by imaging the progression of disease (e.g., the location(s) and size(s) of tumors in cancer, or inflammatory lesions in inflammatory bowel disease) as it is being treated [11].

Additive Electro Spraying (AES), - i.e., integration of electrosprayed nanoparticles into electrospun fiber network – has been also proposed in literature as an interesting route to integrate nanoparticles and fibers by the implementation of a unique process driven by high voltage electric field applied to active loaded polymer solutions, with relevant benefits in terms of resource costs and product feasibility. Because of their large versatility, AES represent a set of high cost–benefit technologies to develop micro and/or nanostructured platforms with improved tunability of molecular release to support cell functions, without altering structural properties of fibers network [12,13].

Conclusion

The research activities aimed to implement the nanomedicine field are growing and leading to the development of highly functionalized multipurpose structures acting as drug vectors or scaffolds for cells cultivation. Electrospinning is one of the nanomanufacturing techniques currently existing for the realization of 3D porous structures composed of nanofibers. Organic, inorganic or composite materials can be easily transformed into nanofibers and combined with biological molecules to augment and customize interactions with the biological environment.

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