Recent advances in biofunctionalization of core–shell fibers produced by coaxial electrospinning make them good candidates for controlled biomolecule and drug delivery.

Advantages and challenges offered by biofunctional core–shell fiber systems for tissue engineering and drug delivery

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Whereas highly porous scaffolds composed of electrospun nanofibers can mimick major features of the extracellular matrix in tissue engineering, they lack the ability to incorporate and release biocompounds (drugs, growth factors) safely in a controlled way. Here, electrospun core–shell fibers (core made from water and aqueous solutions of hydrophilic polymers and the shell from materials with well-defined release mechanisms) offer unique advantages in comparison with those that have helped make porous nanofibrillar scaffolds highly successful in tissue engineering. This review considers the preparation and biofunctionalization of such core–shell fibers as well as applications in various areas, including neural, vascular, cardiac, cartilage and bone tissue engineering, and touches on the topic of clinical trials.

Introduction

An important task of tissue engineering (TE) is the design of scaffold structures that mimic the extracellular matrix (ECM) (*i.e.*, support the reproduction of tissue at the cellular scale and provide templates for the macroscopic shape of the target tissue). Corresponding scaffolds have been prepared using a variety of techniques, including nanofiber- and microfiber-based scaffolds, which turned out to have great potential. These are produced by electrospinning [1–3] yielding fibers with diameters in the range of sub 100 nm up to a few micrometers. Small fiber diameters present large specific surface areas highly favorable for cell adhesion processes and for presenting biofunctional motifs. The longitudinal character of fibers induces contact-guiding effects for cells, and the scaffolds are highly porous with total porosities of up to 90%, which favors permeation, diffusion processes of gases and fluid media but also the in-growth of cells.

Electrospinning itself adds a set of further favorable features. One is that a broad range of natural and synthetic materials can be spun into monolithic fibers but also into more-complex fibers, such as core–shell, Janus-type or tri-layer systems, which are discussed below. Furthermore, electrospinning allows the induction of specific orientational architecture, such as random fibers

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or uniaxially oriented fiber arrangements. However, electrospun scaffolds possess some serious limitations with respect to tissue engineering applications. Biofunctional molecules introduced into the monolithic (*i.e.*, compact) fibers are either homogeneously distributed within the solid matrix or located in phase-separated regions enclosed by the solid matrix. Such environments frequently endanger their bioactivity and a controlled release of biocompounds can also pose problems. This is where core–shell fibers produced by coaxial electrospinning come into play [4–7]. Core–shell fibers offer the same set of favorable features for scaffolds as monolithic fibers. They also add novel features of direct interest for biomedical applications. These include the possibility of producing the core from fluid materials, including water or aqueous polymer solutions, providing favorable environments for biocompounds. Biocompounds of different compositions can also be incorporated separately into the core and the shell in a controlled way during spinning and the release kinetics can be adjusted *via* structural features concerning the core and the shell. Furthermore, the shell material can be chosen in such a way that it directly provides cell-adhesive motifs. The advantages of such features for biomedicinal applications together with the related challenges are presented below.

Principles of monolithic and core–shell fiber formation through electrospinning with a view to biomedicinal applications

Monolithic fibers

Electrospinning constitutes a versatile technique for the production of fibers with diameters from several micrometers down to a few nanometers [8–11]. It involves the formation of solid fibers from polymer solutions but also from melts without any mechanical forces, simply by the application of a high-voltage electric field. Electrospinning set-ups consist, in general, of four major components: a high voltage power supply; a feeding system for the fluid polymer stream, for instance a pump; a spinneret or nozzle; and a collector for the solid fiber, with the voltage being in most cases applied between the nozzle and the collector. More-complicated set-ups exist and have been detailed in the general literature [9]. A pump or nozzle arrangement is a typical laboratory set up.

Detailed theoretical and experimental investigations have identified the following key processes.

- Droplet deformation at the nozzle with a subsequent onset of fluid stream, a jet directed toward the counter electrode.
- Longitudinal stretching deformation of the rectilinear jet.
- Onset of transverse bending deformations with looping, spiraling trajectories in which the jet continues to be strongly elongated.
- Deposition of solid fibers (as a result of cooling or solvent evaporation) on counter electrodes and/or substrates.

The deposition gives rise, in general, to fibers randomly oriented in the plane of the membrane. Yet, by using rapidly rotating counter electrodes or configurations with sets of parallel electrodes, scaffolds are obtained in which the fibers are oriented in a uniaxial manner. The required type of fiber orientation is dictated by the biomedical application in mind. The range of parameters known to affect electrospinning of nanofibers and corresponding nonwoven fibers is extremely broad [8,9]. One feature of significant interest as far as biomedicinal applications are concerned is the fiber diameter, which not only controls the total surface area but also the pore sizes in the membranes and thus the tendency toward cell in-growth.

Core–shell fibers

Scaffold architecture accessible by electrospinning has become strongly extended since the introduction of coaxial electrospinning in 2003 [4]. Coaxial electrospinning has made significant progress in terms of fiber structures achieved, modifications to which it has been subjected and in terms of modeling and experimental developments [6,7,9]. In coaxial electrospinning, in principle, an inner and outer nozzle arranged in a concentric geometry, able to pump two different spinning solutions simultaneously, are used to produce a core–shell droplet at the nozzle exit (Fig. 1a) [4,6]. At sufficiently strong electric fields a compound fluid jet emerges from the tip of the deformed droplet. Further down its path the compound jet experiences the bending instability known in conventional electrospinning, inducing strong jet stretching and jet thinning. Finally, a thin solid core–shell fiber is deposited on a substrate (Fig. 1b). The range of materials selected for the preparation of the core has become extremely broad, for example hydrophilic fluid systems with the shell material tending to be of a polymeric nature, including natural and synthetic polymers. The feeding rates for the formation of the core and shell as well as the respective compound concentrations in the feeding fluids are control parameters for the radius of the core and the thickness of the shell. Simulations have revealed that in the presence of an applied field the electric charges concentrate at the outer surface of the compound droplet and jet, respectively, so that biocompounds in the core are protected against electric charges.

Applications of coaxial electrospinning evaluated in the literature include the encapsulation of nonspinnable polymers and nonpolymeric materials, such as drugs, or biologically active objects in the fiber core characterized by controlled-release kinetics. It is important to emphasize that biologically active molecules are protected in core–shell systems from organic solvents used for spinning the shell.

Toward more-complex systems

Interesting approaches involving fibers with complex architecture include the preparation of Janus-type fibers and fibers characterized by three layers, as obtained by triaxial electrospinning. An example is the use of ethyl cellulose (EC) to produce such fibers with all three layers composed of EC yet containing increasing concentrations of the model drug ketoprofen, (*RS*)2-(3-benzoylphenyl)-propionic acid (KET), which is a nonsteroidal anti-inflammatory drug, from the outer to the inner layer [12]. This specific arrangement is found to give rise to a linear release of the drug extending over 2 h.

Biofunctionalization of electrospun core–shell fibers

Surface and bulk biofunctionalization

Key issues in the design of scaffolds for tissue engineering are, firstly, the interactions of the cells with the scaffold substrate. These interactions can be controlled by providing specific biochemical motifs on the fiber surface. Secondly, the need exists to provide specific bioactive molecules in the environment of these cells, such as growth factors, to control the fate of the cells, such as