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Electrospun Nanofibers as Carriers for Bioactive Molecules

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Nanofibers are valued for their ultra-high specific surface areas (i.e. surface-to-volume or surface-to-mass values), and have been found potentially useful in many biomedical applications, such as wound dressing and scaffold for tissue engineering [1-3]. Modification or functionalization of nanofibers is necessary in order to engineer specific features that will help maximize their end-use performance. A spectrum of bioactive molecules, including antibacterial agents, anti-cancer drugs, enzymes, proteins, can be incorporated into nanofibers via different approaches.

Nanofibers Loaded with Antibacterial Agents

Oral administration and venous injection are the most frequently used methods for drug delivery, but may not be the most efficient ways in some situations. For example, patients with severe burn wounds or skin ulcers usually require antibiotics for infection control. However, with systemic administration of the antibiotics the patient may run the risk of renal or liver toxicity, or only an insufficient portion of the prescribed drug reaches the wounded tissues [4]. Furthermore, the ischemic wounds with little granulation tissues (i.e. newly formed vascular tissue normally produced during healing of wounds) can hardly be penetrated by the drug. In these situations topical administration may function as a remedy [4-6], with which the antibiotics are applied in minimal amounts at the site of infection and make sure that they function efficiently there. Accordingly, nanofibers with incorporated antibiotics have been studied as potential potent materials for wound care [7,8]. Similarly, a lot of work has been concentrated on the development of nanofibers loaded with anti-cancer drugs, which, when topically administered, may help constitute a remedy for the many side effects (e.g. toxicity to healthy cells) and low efficiency that go with current chemotherapy.

Silver ions have long been known for its antimicrobial capacity. These positively charged ions are readily bound to the negatively charged proteins to favor precipitation and denaturation. Products with various silver compounds, including silver nitrate and silver sulphadiazine, have been developed for wound care [9]. However, there have been concerns about the toxicity caused by the large excess amounts of silver released from the dressing and harmful to the wound [10]. Reasonably, efforts have been made to develop dressing products capable of sustained release of silver ions so that wound dressings can be less frequently changed and efficacy of infection control enhanced. Among those efforts, nanofibers have been frequently adopted as a potential efficient drug carrier for the silver (usually in the form of nanoparticles). Two approaches have been used to prepare a silver-polymer nanofibrous structure: the *in situ* and *ex situ* methods. With the *ex situ* approach, nanoparticles are produced first and then dispersed into the polymer matrix to form a composite structure. However, this process may make it difficult for the silver nanoparticles to distribute into the polymer matrix in such a way that they can be expected of their best efficacy, as the nanoparticles may easily be aggregated with each other to form clusters [11]. Alternatively, *in situ* approach consists of electrospinning of the mixed solution of a silver salt (or compound) and a polymer, followed by a reductive reaction to yield silver nanoparticles within the nanofiber structure [12].

Generally speaking, if both the drug(s) and the polymer can be dissolved in a single solvent, they can be co-electrospun into nanofibers from a mixed solution of the drug(s) and the polymer [13]. Otherwise, for drugs that are not soluble in any of the solvents for the polymer, or can be destroyed by organic solvents, there are two options: emulsion electrospining and coaxial electrospinning.

- For emulsion electrospinning, an aqueous solution of the drug is emulsified in a polymer solution to form a water-in-oil (w/o) emulation (i.e. a mixture of two immiscible liquids, one of which is an aqueous solution and dispersed as microscopic or ultramicroscopic droplets throughout the other oily solution), and the emulsion is electrospun. This approach produces electrospun nanofibers with a core/sheath composition: the drug is encapsulated in the core and the polymer serves as the sheath [14].
- In coaxial electrospinning, use is made of a special coaxial spinneret [15]. Two coaxial capillaries allow the electrospinning of two components simultaneously: solution (either in water or organic solvents) of the medication in the core capillary, and the polymer solution in the outer capillary, hence the fabrication of nanofibers also of a core/sheath structure: the medication in the core and the polymer on the surface [16].

Nanofibers prepared via emulsion or coaxial electrospinning usually has a core/sheath structure, the fiber-forming polymer comprising the sheath and the drug(s) encapsulated in the core. Such a structure provides sustained release of drugs from the nanofiber drug carrier.

Nanofibers Loaded with Other Bioactive Molecules

Nanofibrous structures have been identified as an excellent choice for scaffolds in tissue repair and regeneration. In these applications, there must be a favorable environment for the cells to attach to the scaffold, to migrate, to proliferate and to differentiate into the target tissues. To that end, the scaffolds should have appropriate physical properties, including high porosity, structural stability, controllable degradability, and, if necessary, desirably tailored orientations. Furthermore, the scaffolds are expected to provide an optimum biochemical environment for the growth of the cells/tissues. Most of the bioactive agents able to guide or stimulate the cellular activities (e.g. the growth factors) are proteins that have larger molecular weight (i.e. over tens of thousands) than the drugs (usually hundreds to thousands)

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as discussed in the previous section. Hence the extensive studies on the incorporation of such bioactive agents into/onto the nanofibrous structures.

Proteins contain both acidic (e.g. carboxyl/-COOH) and basic (e.g. amine/-NH_2) functional groups, which combine to decide the overall charge of a protein molecule (e.g. positively or negatively charged). It follows that a polyelectrolyte (i.e. a charged macromolecule formed in an aqueous solution by dissociation of its charged units), like chitosan, may have its advantage as a nano-carrier for the bioactive protein, because electrostatic interactions between the polymer and protein help to entrap the protein into the nanofibrous structure [17].

Different methods have been adopted to incorporate proteins into nanofibers. If both the bioactive agents and the polymer can be dissolved in a single solvent, they can be co-electrospun into nanofibers from a mixed solution [18]. Otherwise, co-axial electrospinning will be the option, with which nanofibers of the core/sheath structure are produced, usually with the bioactive agent(s) in the core and the polymer as the sheath. This structure has become well-known for its capacity to make for sustained and prolonged release of bioactive agents from the drug-carrier than nanofibers incorporated with randomly dispersed bioactive agents [19].

Another alternative method is to immobilize bioactive proteins onto the fiber-forming polymer via the zero-length cross-linking agents, EDAC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride) and NHS (N-hydroxysulfosuccinimide), which may be removed completely after the reaction [20]. Such functionalized nanofibers with bioactive agents immobilized on their surface have been demonstrated to be effective in promoting cell adhesion, proliferation, and differentiation or wound healing [8,21,22].

Conclusion

Electrospun nanofiber is becoming an interest in biomedical applications. Electrospun nanofiber scaffolds provide temporary spaces with tunable porosity for cells to grow and exchange metabolites/nutrients with their environment. They can also be fabricated as a drug carrier to release therapeutic agents to wounds in a controlled manner, rather than using direct injections of drugs of high cost and low efficiency. Co-axial and emulsion electrospinning produce nanofibres with sheath-core structures and provide a more sustained release of drugs. Nanofibres can be immobilized with a variety of regulators (like growth factors) to change cell fates. Despite much research on functionalized nanofibres, there has been little work on the development of nanofibres having more than two incorporated bioactive molecules. However, multi-functions are desirable for the application of nanofibres in wound healing to protect the wound from infection, to inhibit non-specific adsorption, and to promote tissue reconstruction.

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