

# Nanofibers As Implantable Controlled Release Systems

Serim TM<sup>1</sup>, Eren-Boncu T<sup>2</sup>, Amasya G<sup>1</sup>, Sengel-Turk CT<sup>1</sup> and Ozdemir AN<sup>1\*</sup>

<sup>1</sup>Department of Pharmaceutical Technology, Faculty of Pharmacy, Ankara University, Turkey

<sup>2</sup>Department of Pharmaceutical Technology, Faculty of Pharmacy, Erciyes University, Turkey

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**\*Corresponding author:** A Nurten Ozdemir, Ankara University, Faculty Pharmacy, Department of Pharmaceutical Technology, Ankara, Turkey

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## Introduction

Controlled release systems that release the active substance at the desired rate for the desired time have been developed to reduce the incidence of side effects seen in treatment with classical dosage forms and to increase the compliance of the patients with the treatment by reducing the frequency of drug use. Controlled release systems are systems in which the release time and rate are adjusted according to the desired purpose, and the active substance can be targeted to a specific area of the body. Controlled release systems have many advantages over conventional systems such as improved efficacy, reduced toxicity, and better patient compliance [1]. The most ideal route of administration for controlled release systems is to implant dosage forms in the desired area of action. In the treatment with implantable controlled release systems; a) The treatment efficiency increases, and the side effects observed in the systemic drug delivery are eliminated as the delivery of the active substance is provided in the desired area, at the desired dose and for the desired time. b) Plasma concentration can be kept in the therapeutic range without fluctuation for a long time, since they release the active substance at a controlled rate. c) Problems seen in the absorption and distribution of the active substance in conventional dosage forms are eliminated. d) The risk of systemic side effects decreases as there will be a high concentration of active substance in the area of effect but very little active substance in other organs, since the implant is directly placed to the area where the therapeutic effect is desired. e) The possibility of forgotten doses decreases, patient compliance increases, auxiliary health personnel are not needed for drug intake, and treatment efficiency increases since there is no repetitive drug intake. Implantable delivery systems can be prepared in forms such as films, nanoparticles and microspheres, and the latest technology developed as implantable delivery systems is nanofiber technology.

## Mini Review

Nanofibers are nontoxic and biocompatible drug delivery systems, that vary in size from nanometer to micrometer, have large surface area per unit mass compared to other pharmaceutical forms (for example, ~100 nm diameter nanofiber has a specific surface of 1000m<sup>2</sup>/g) and high surface-to-volume ratio, high porosity, superior flexibility and mechanical properties [2-5]. Compared to other dosage forms, they are systems that provide effective drug release due to their large surface area [6] and have higher encapsulation efficiency compared to spherical nanoparticles [6,7]. Nanofibers can be made into pharmaceutical dosage forms capable of rapid, delayed and controlled release. Nanofibers, which increase clinical efficacy by improving biopharmaceutical properties, also carry the advantages of classical solid dosage forms such as easy processability, stability and ease of transportation and storage [8-12]. Nanofibers, which provide cell growth and proliferation, are widely used in tissue engineering as medical prosthesis and tissue support, as well as in wound and burn treatment [13]. Nanofibers can be used in soft tissue prostheses such as vascular and breast, as well

as adsorbed in the form of thin, porous structures on hard tissue prostheses implanted in the human body, and it is considered to be used as post-operative implants [6,14]. One of the biggest problems in the design of biomaterials to be applied to tissues is that these structures must be similar to the extracellular matrix [6]. Almost all human tissues and organs, including bone, teeth, cartilage, collagen and skin, are fibrous. In addition, cells perceive small and unsimilar materials as foreign matter and phagocytize them [3]. Due to being fibrous and nano-sized, electrospun nanofibrous structures can imitate the extracellular matrix, adapt to the tissue, are protected from phagocytosis, and trigger cell growth and proliferation with this size and shape [15]. In studies, fibers with diameters ranging from 3 nm to 1 $\mu$ m were produced with more than 50 polymers, and it has been shown that this method is suitable for both hydrophilic and hydrophobic active substances [6]. It is known that by implanting electrospun implants into the tissue, they provide localized, long-term, controlled release of active substance and are superior to the preparations in the market [16]. The study, which showed that nanofiber formulations produced for the delivery of tetracycline HCl with Polylactic Acid (PLA), Polyethylene Vinyl Acetate (PEVA) and Poly (Lactic Acid-Co-Glycolic Acid) (PLGA) 50:50 mixtures were superior to the commercial preparation, is one of the earliest promising studies to show that these systems can be used as drug delivery systems [17]. In studies, where it was observed that the formulations of sustained-release paclitaxel-loaded PLGA electrospun nanofiber implants had an API release for 60 days in vitro and the formulations prepared for application to the tumor tissue in the brain in post-operative glioma chemotherapy had a controlled release for 24 days in vivo, it was proven that the nanofiber implant was superior to Taxol, which is the intravenous commercial product [16,18]. Nanofibrous structures have been formed with many polymers such as Poly-L-Lactic acid (PLLA), Polycaprolactone (PCL), PLGA and chitosan [13, 19-23].

The compatibility of the active ingredient/polymer/solvent is very important for the preparation of controlled release nanofibers. In the study, in which electrospun PLLA fibers were produced with lipophilic paclitaxel, hydrophilic doxorubicin hydrochloride and lipophilic doxorubicin base, it has been found to have good encapsulation and release with zero-degree kinetics since paclitaxel is compatible with PLLA and dissolves in chloroform/acetone solvent [24]. A polymer suitable for the active substance must be used in order to encapsulate most of the active substance into the fiber and to provide a continuous and stable release profile, and the solvent used must be compatible with both the polymer and the active substance [24]. When nanofiber formulations with different antibiotics were implanted, antibiotics were observed above the minimal inhibition concentration around the implantation site for a long time, while the concentration in the bloodstream was quite low and the risk of side effects seen when antibiotics were given by other administration routes was reduced [25,26]. There are also studies on the use of antibiotic-loaded nanofibers for local effect by adsorbing them to vascular grafts or prostheses on the market [25,27]. In these studies, while most of the active substance

is encapsulated into the material, some adsorbing to the surface causes the burst release, and it has been observed that it has a positive effect in the treatment of bacterial infections by allowing microorganisms to be exposed to high doses of antibiotics at the beginning [27,28]. As a result of in vitro and in vivo experiments, although there is very little active substance left in the adsorbed material and on its surface, the presence of a high concentration of active substance in the tissues around the material has proven that local effect is achieved by preventing the systemic side effects of the active substance [27]. It has also been observed that metronidazole/PCL nanofibers reduced inflammation compared to PCL nanofibers when applied as a subcutaneous implant, inhibited anaerobic bacterial growth and maintained these effects for 2 weeks [29].

There are many methods for the production of polymeric nanofibers. These are: The drawing technique, template synthesis, phase separation, self-assembly and electrospinning. Electrospinning was patented in 1934 and applied in many fields, especially tissue engineering [13]. Among the nanofiber preparation methods, electrospinning method was determined as the most suitable method because products with a wide range of fiber diameters can be obtained uniformly by changing the formulation and system parameters, it is a one-step method that does not require expensive purification processes and it provides reproducible data, it is suitable for scale-up, and it allows production with many polymers and solvents [6,30,31]. Electrospinning is a method of increasing interest in tissue engineering and controlled drug release globally since it can form structures from micro to nano size with high porosity, resembling the extracellular matrix. This method basically requires 3 components:

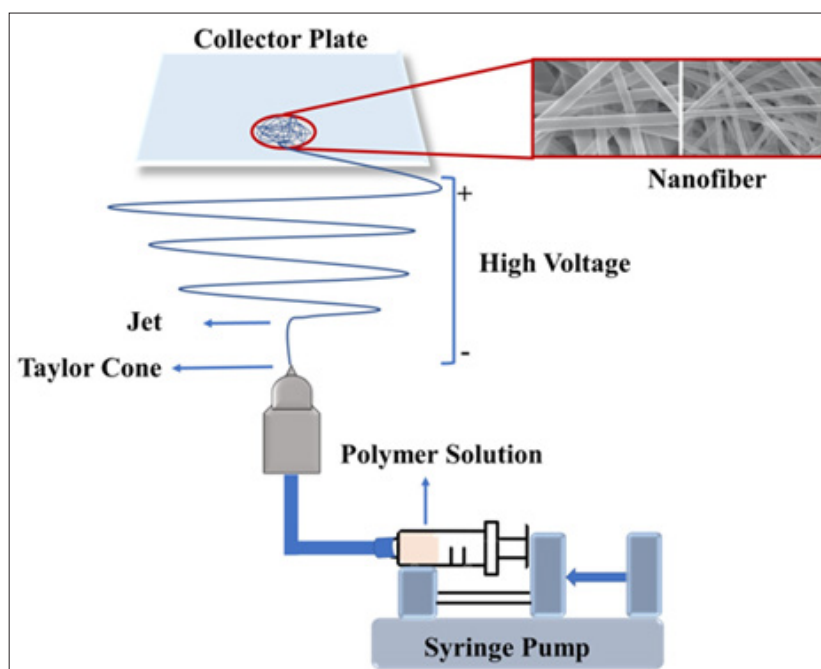
- a. High voltage source (around 30kV)
- b. Needle
- c. Collector metal plate

While performing the electrospinning process; The polymer solution is filled into the injector and connected to the electrospinning needle after the injector is placed in the pump. The distance between the needle and the collector plate is adjusted and high voltage is applied between the needle tip and the collector plate with the help of the power supply. When the system reaches the critical voltage value, the polymer solution is sprayed from the injector. The droplet at the needle tip is deformed due to the electrostatic attraction of the counter electrode just before the surface tension is overcome. The cone shape formed at the needle tip of the drop is called the "Taylor Cone" [32,33]. The polymer solution that reaches this value is electrically charged positively and moves towards the negatively charged collector. Meanwhile, the solvent in the polymer solution evaporates, forming structures called electrospun fibers with very fine fibers on the metal collector plate. The critical parameters in the electrospinning process are:

- a. Selection of the appropriate solvent system for the polymer;

- b. Having an appropriate solution viscosity and surface tension,
- c. Determining the flow rate that will enable the Taylor cone to form,
- d. Application of the optimum voltage,
- e. Setting of the appropriate distance for the solvent evaporation [2,31,34].

In the production of electrospun polymeric fiber, the physical and mechanical properties of the nanofiber and its chemical properties, including the degradation rate, can be changed by optimizing the parameters such as voltage, polymer-solvent systems, distance between the injector and the collector plate, pump speed, injector inner diameter, etc. Nanofibers with desired properties can be produced with many materials, including polymers, biopolymers, DNA, proteins, and even macromolecules such as phospholipids. The illustration of electrospinning method is given in Figure 1.



**Figure 1:** Schematic illustration of the electrospinning method.

## Conclusion

In recent years, the use of polymeric nanofibers has gained great importance in biomedical and biotechnological applications such as tissue engineering, controlled release systems, wound dressings, medical implants, composites for dental applications and biosensors. Among the different nanofiber preparation methods, the electrospinning method is the most preferred production method because it allows the production of nanofibers with different materials, from natural or synthetic polymers to ceramics, and allows cheap, simple and fast production. Polymeric nanofibers are promising drug delivery systems, especially in terms of their applications as controlled release systems to achieve localized drug delivery.

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