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REVIEW PAPER

Electrospinning applications in neurological diseases

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ABSTRACT

Neurological diseases represent a spectrum of complex disorders characterized by degradation of nerve cells or nerve tissue within the nervous system. Currently, optimal therapeutic interventions for neurological diseases as a significant threat to human health are lacking. Electrospinning, as a widely used nanotechnology methos, is capable of producing a wide range of micro- and nano-structures with the excellent structure, high specific surface area, and superior drug loading capacity. It also provides the solution properties including viscosity, elasticity, conductivity, and surface tension. The improvements of electrospinning devices can be achieved by controlling variables including voltage, zeta potential, distance between electrospinning nozzle and the collector, and also, environmental parameters including temperature and humidity. Hence, electrospinning could mimic the complex neural tissue structure, regulate the behavior of neuronal cells, and even deliver the drugs across the blood-brain barrier, showing excellent application prospects in neurological diseases. In this review, we summarize the recent improvements of electrospinning and the recent applications of electrospinning in neurological diseases, hoping that it may provide the valuable insights for researchers in the field of nanomaterials.

Keywords: *Electrospinning, Electrospinning nanofibers, Improvement and application, Neurological diseases*

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INTRODUCTION

Neurological diseases are a type of complex diseases in which nerve cells or nerve tissue in the nervous system are injured or damaged. Neurological diseases are mainly characterized by sensory, motor, consciousness, and autonomic dysfunction in the central nervous system, peripheral nervous system, and autonomic nervous system. To date, a wide range of neurological diseases have been identified, including meningitis, stroke, traumatic brain injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis, and idiopathic epilepsy [1]. The symptomatology of these neurological diseases tends to be complex and varies according to the type and location of the affected area, often resulting in overlapping clinical manifestations, making these conditions acute or severe in nature. It is reported that nearly one billion people worldwide suffer from neurological diseases in the world, and the cost of neurological diseases accounts for 7.1% of the total global disease burden. Currently, there are no ideal drugs or treatments for neurological diseases, which seriously threaten human health and quality of life [2, 3].

Electrospinning is a kind of innovative nanotechnology with the capability to produce a variety of nanofibers, bead fibers, and microparticles with the diameters ranging from tens to hundreds of nanometers and different porosity and large specific surface area [4]. Because the advantages including simple operation and low cost, electrospinning technology can spin many kinds of materials to obtain many kinds of electrospinning fibers or microparticles [5, 6]. This products with different patterns can mimic the complex nerve tissue and encapsulate one or more neurotrophins or neurotherapeutic agents via various electrospinning techniques, which proves the great potential of electrospinning in neurological therapies [7]. In this review, we summarize the latest improvements in electrospinning technology and its recent progress in neurological applications from the Web of Science database, Scopus database, and Pubmed database, providing valuable insights

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for researchers in this field.

Improvement of electrospinning

Electrospinning technology is the process of spinning polymers from solid or

liquid state into electrospinning fibers or electrospinning nanoparticles through Taylor cone under the high voltage (this kind of high voltage can range from several thousand to tens of volts). Electrospinning equipment mainly includes syringe pump, syringe, power supply, and collector. These different parts of electrospinning apparatus can be diverse. They can be combined with the different electrospinning environments including polymer characteristics, electrospinning temperature, and electrospinning humidity to obtain fibers with various properties and functions in a wide range of interdisciplinary fields.

Improvement of syringe pump

Syringe pump as one of part of electrospinning apparatus is mainly used to accurately push polymer solution from syringe into electrostatic field for electrospinning. It can accurately and stably transport electrospinning to ensure the stable production of electrospinning fibers. Generally, the speed and accuracy of syringe pump can directly affect the quality of electrospinning nanofibers. To obtain electrospinning nanofibers with different functions and characteristics, there are several kinds of improvements of syringe pump, including single channel syringe pump, dual channel syringe pump, multichannel syringe pump, dual channel single control syringe pump, and multichannel single control syringe pump [8, 9]. To meet the low temperature requirements of some polymers or proteins, there are also temperature control syringe pumps. Due to the complexity and specificity of the structure of the nervous system, these different deformations or modifications of syringe pump, can result in the electrospinning fibers with the specific functions and properties to alleviate the symptoms of neurological disorders (Fig. 1).

Improvement of syringe

Syringe as a connection between a syringe pump and an electrospinning nozzle is mainly used to temporarily store electrospinning solution. At the same time, this kind of cylindrical shape syringe can prevent solvent evaporation to maintain the basic properties of electrospinning solution. In recent years, electrospinning syringe has also made many improvements to meet different needs. For example, Seongjun Moon, et al. developed a kind of syringeless electrospinning technique with helically probed rotating cylinder to improve the electrospinning yield and expand the electrospinning application materials. This kind of helically probed rotating cylinder contained many integrated needles with the diameter at 0.1-1.0 mm, which produced the higher yield of electrospinning nanofibers with excellent performance [10]. To solve the disadvantages of colloidal electrospinning including few kinds

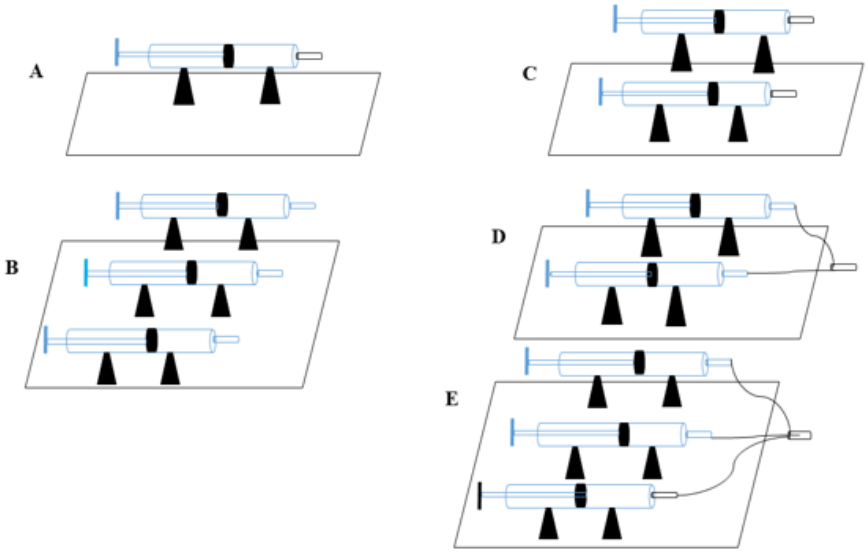

Fig. 1. The schematic diagram of the different types of syringe pump improvements. A: single channel syringe pump; B: multichannel syringe pump; C: dual channel syringe pump; D: dual single control syringe pump; E: multichannel single control syringe pump.

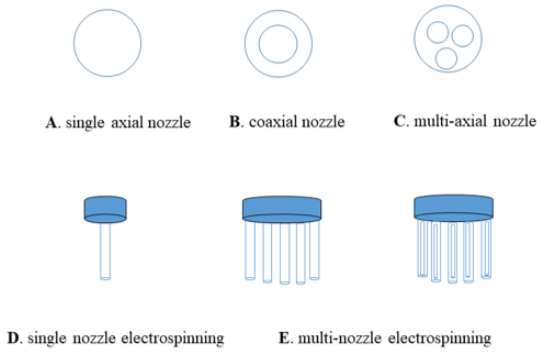

Fig. 2. The schematic diagram of the different types of electrospinning nozzle improvements

of polymers that can be used for colloidal electrospinning, and problems of the lower yield, Jaeyu Lee, et al. developed a special rotating drum instead of the conventional collector. This kind of rotating drum reduced the precipitation of inorganic fillers in the electrospinning solution. The experimental results demonstrated that the syringeless electrospinning easily increased the electrospinning yield; and it could be successfully applied to multiple electrospinning schemes [11, 12]. Similarly, to solve the problem of nanoparticle precipitation during the electrospinning, Federico Trupp, et al. designed a kind of novel rotating syringe to prevent the sedimentation of nanoparticles in the electrospinning solution. The results proved that the encapsulation rate of 42±7 μm indium microparticles in poly(vinylidene fluoride) (PVDF) solution increased to 400% compared with the traditional electrospinning without the special rotating syringe system [13]. In conclusion, these specific improvements of the electrospinning syringe can increase the yield and quality of electrospinning fibers, which could effectively treat neurological diseases.

Improvement of the electrospinning nozzle

Electrospinning nozzle as one of the core components of electrospinning technology is the simplest and most improved part in the electrospinning. Because not only the diameter and length of the electrospinning nozzle itself can determine the basic characteristics of the electrospinning fibers, but also the distance between the electrospinning nozzle and the collector, the electrospinning environment, and the electric field can improve the characteristics of the electrospinning fibers. According to whether there is an electrospinning nozzle, electrospinning technology can be classified into conventional electrospinning and nozzle-free electrospinning [14]; according to the classification of nozzle structure, electrospinning nozzle can be divided into single axial nozzle, coaxial nozzle [15, 16], coaxial dual layer nozzle [17], and multi-axial nozzle [18]; according to the number of nozzles, electrospinning can be divided into single-nozzle electrospinning and multi-nozzle electrospinning [19] (Fig. 2). Considering whether external forces are needed for classification, electrospinning can be classified into bubble electrospinning [20], centrifugal electrospinning [21, 22], magnetic field-assisted electrospinning [23] and gas-assisted electrospinning [24]. The advantages and disadvantages of the latest classification are summarized in Table 1. These improvements of the electrospinning nozzle can result in the high-quality electrospun fibers closer to neural structures or neurological function, beneficial for the recovery of neurological diseases.

Improvement of electrospinning collector

Electrospinning collector is another device with the various improvements in electrospinning technology. In general, electrospinning products with different shapes and functions can be obtained by improving the electrospinning collector to meet different needs. For example, Jin Yeong Song, et al. invented a kind of 3D ear cartilage-shaped hydrogel collector to obtain the conformal electrospun nanofiber mat with

Table 1. The advantages and disadvantages of the different kinds of electrospinning types

Electrospinning type	Advantages	Disadvantages	Ref.
Bubble electrospinning	Reduce static electricity pollution and increase production	Hard to control the bubble's size and number; the surface charges of bubbles	[25, 26]
Centrifuge electrospinning	Efficiently produce the ultrathin polymer nonwoven meshes	Special accessories; difficult to operate	[27]
Magnetic-field-assisted electrospinning	produce highly aligned nanofiber	High requirements for material types and difficulty in industrialization	[28]
Gas-assisted electrospinning	Uniform diameter of electrospining fibers; reduce the electrospinning fiber breakage	Special accessories; difficult to operate	[29, 30]

specific 3D structure, which could overcome the influence of the complex structure with irregular concave and protruding areas to obtain the conformal shape-specific nanofibers mat with the same thickness [31]. To achieve high-performance 3D electrospinning nanofiber scaffold with excellent load-bearing capacity, Fatemeh Hejazi, et al. designed a kind of helical spring-shaped collector, depending on this special collector, they obtained a kind of 3D porous electrospinning PCL nanofiber scaffold with better morphological and mechanical properties [32]. To attain a small caliber electrospinning vascular scaffold that is close to the real vascular physiological structure, Hao-Yang Mi, et al. spun the thermoplastic polyurethane /polycaprolactone through a kind of modified rotating collector, and obtained the excellent biocompatible electrospinning scaffold with 1-3 mm lumen diameter and 100-570 μm wall thickness [33]. Similarly, Eom S et al. acquired the complex nanofiber scaffold through the 3D hydrogel collector, and found that this kind of hydrogel collector possessed the advantage of concentrating the electric field to the great extent compared with the metal collector [34]. With the emergence of various improvements of the electrospinning collector, electrospinning fibers that are finer and closer to the neural structure and function can be obtained.

Application of electrospinning to neurological diseases

Electrospinning is a kind of diversified nanotechnology for producing different types of electrospinning nanofibers with special morphology, function, and structure. These special electrospinning nanofibers have the unlimited application potential in neurological diseases. In general, electrospinning is mainly applied to nervous system diseases in two ways: (1) to mimic the physiological structure or physiological function of nerve tissue. For example, according to the electrophysiological characteristics of nerve cells, Zhang H, et al. produced a silk fibroin/ PVDF electrospinning scaffold loaded with the conductive MXene by electrospinning. They found that the special electrospinning mat could improve the proliferation the Schwann cell. Also, the animal results demonstrated that the conductive scaffold had the effect on the elongation and myelination of axon, which exhibited the excellent performance on peripheral nerve injury [35]. Samadian et al. designed a nerve guide conduit made by PCL/ gel by electrospinning. After evaluation, it was found that the electrospun nerve guide conduit had the motor and sensory functions [36]. Chen et al. obtained a biodegradable electroactive 3D piezoelectric PLA electrospinning mesh with the characteristic of ultrasound-induced electrical stimulation. The results of animal experiments verified that this kind of electrospinning mesh could advance the motor functions and alleviate the symptoms of spinal cord injury [37]. To mimic the nerve tissue structure, Li et al. invented an electrospinning nervous tracts including multi-layered nanofibrous yarns through a mortified electrospinning fabrication technology. This kind of artificial electrospinning nervous tracts had the high similarity in structure to natural nervous tracts, and could progress the axon regeneration and neural function recovery [38]. In particular, Zheng et al. electrospun the longer PLLA-aligned nanofibers and mortified them by pDNM gel to obtain nerve guidance conduits. The animal experiments validated that this kind of nerve guidance conduits could improve the number of axon and nerve fiber myelination, which may provide an application potential for peripheral nerve injury [39]. In particular, Xu et al. designed a kind of biologically active oriented electrospinning fibers, which encapsulated the brain-derived neurotrophic factor (BDNF) and could mimic the 3D structure of the nervous system by microsol electrospinning. This kind of special electrospinning fibers increased the transplantation rate and the differentiation efficiency of stem cells. Also, it reduced the inflammatory response of stem cells by activating integrin β1 and anti-inflammatory genes, showing the excellent palliative effects on spinal cord injury [40]. Guan et al. electrospun a kind of special silk fibroin encapsulated metformin by micromolding electrospinning with the excellent micro-nano structure. This kind of special electrospinning fibers could increase the expression of neuron-related genes and improved the neuron behavior [41]. (2) To load or encapsulate factors or drugs with neuroprotective effects to repair injured nerve cells or promote nerve cell growth. These special electrospinning fibers for encapsulating neurotrophic factors and neurotherapeutic drugs have sustained drug release and good biocompatibility, which can be well applied to the treatment of neurological diseases. For example, Tseng et al. prepared a type of vancomycin-loaded poly [lactic-co-glycolic acid] (PLGA) electrospinning fibers by conventional electrospinning, which could continuously release vancomycin for 8

Table 2. The recent progress in the electrospinning applications in neurological diseases

Polymer	Fiber type	Electro-spinning type	Types of drug encapsulation	Therapeutic effect	Neurological disease type	Ref.
PLGA	Randomly	Conventional	Vancomycin	Decrease cerebral infections	Postoperative infections in brain	[42]
PCL	Aligned	A two-pole airgap electrospinning	A cocktail of miR-132/miR-222/miR-431	Promotes functional recovery and remyelination	Spinal cord injury	[43]
PLA	Core-shell	Conventional	Docosahexaenoic acid	Reduced neuron loss and increased serotonergic nerve sprouting	Spinal cord injury	[44]
Zein	Randomly	Conventional	Quercetin	Recovered the motor function of the sciatic nerve	Induce mononeuropathy	[45]
ALG/PEOs	Randomly	Conventional	RC-33	Promote cell growth	Spinal cord injury	[46]
Chitosan	Aligned	Electrospinning with a circular collector	RGI peptide and KLT peptide	Enhanced nerve regeneration,promoted vascular penetration	Peripheral nerve injury	[47]
PLLA and PLGA	Randomly	Co-axial electrospinning	Ibuprofen (Ibu) and thyroid hormone triiodothyronine (T3)	Anti-inflammatory and promyelinating efficacy	Vascular and traumatic injuries	[48]
PLA	Randomly	Conventional	Glucagon-like peptide-1 (GLP-1)	Improve expression of the neuronal markers and neurogenesis	Alzheimer's disease	[49]
PVA	Randomly	Conventional	Nek1 protein inhibitor, temozolomide	Decreases GB cells' viability and tumour size	Glioblastoma	[50]
PCL and PLGA	Randomly	Coaxial electrospinning	Self-assembling peptides	Decrease inflammatory response, improve the NSC differentiation	Spinal cord injury	[51]
Polyvinyl pyrrolidone	Randomly	Conventional	Hesperetin	Increased acetylcholinesterase (AChE) activity, lipid peroxidation, degeneration, and inflammation in the hippocampus	Alzheimer's disease	[52]
PCL	Randomly	Conventional	Uric acid	Protected neurons and decreased ROS generation	Spinal cord injury	[53]
PCL and PLGA	Randomly	Coaxial electrospinning electrospray technique	Temozolomide and nimorazole	Slow release	Glioblastoma	[54]
PLGA	Aligned	Conventional	Monosialotetrah exosylganglioside	Improve neuronal viability, neurite outgrowth, and synapse formation	Traumatic brain injury	[55]
PCL/PSA/MP	Randomly	Conventional	Polysialic acid	Promote axonal growth and enhance the functional recovery	Spinal cord injury	[56]
PCL	Randomly	Coaxial electrospinning	Hyaluronic acid methacryloyl (HAMA)/ IGF-1	Prevent cerebrospinal fluid leakage, maintain normal intracranial pressure	Traumatic brain injury	[57]
PLGA	Randomly	Coaxial electrospinning	FGF-2	Promoted locomotor recovery	Spinal cord injury	[58]
PLGA	Randomly	Coaxial electrospinning	Yalproic acid	Increased functional recovery	Spinal cord injury	[59]
PLA	Aligned	Combining electrospinning	Eumelanin	Control of inflammatory response	Spinal cord injury	[60]
PCL	Aligned	Coaxial electrospinning	Bletilla striata polysaccharide	Increased functional recovery	Peripheral nerve repair	[61]

weeks in the animals and promote neural tissue recovery without inflammatory reaction effects [42]. Zhang et al. designed a 3D topographical fiber-hydrogel scaffold by the two-pole air gap electrospinning technique that could deliver miRs. The scaffold could significantly improve the axon regeneration and enhance functional recovery [43]. Liu et al. designed a docosahexaenoic acid-loaded electrospinning fibers by a coaxial spinneret at different flow rates which could release docosahexaenoic acid for 36 days. These fibers rised neurite outgrowth and regulated the expression of brain-derived neurotrophic factor and neurotrophin-3, showing a good performance for spinal cord injury [44]. In general, by improving electrospinning methods, electrospinning fibers, that are closer to the structure of neural tissue and containing multiple neurotrophic factors or neurotherapeutic drugs, could be obtained for application in the treatment of neurological diseases. We summarized the recent progress in the electrospinning application by encapsulating drugs or neurotrophins in Table 2.

Conclusion and prospects

Electrospinning technology has emerged as an increasingly prevalent nanotechnology, owing to its simplicity in operation, expansive range of applications, and superior production efficacy. It has been documented that a wide range of materials, including natural biomaterials, synthetic polymers, and organic or inorganic substances, can be expertly electrospun under various conditions, demonstrating the profound advantages and promising potential of this technique. However, there are still some technical issues that need to be addressed: (1) Difficulty in industrialization of electrospinning. This is the biggest obstacle to the application of electrospinning technology, many scholars have done a lot of work to solve this problem, but the results are not ideal, how to industrially obtain uniform electrospinning fibers is still a problem to be solved. (2) The utilization of organic solvents in the electrospinning process is another concern. The preparation of electrospinning polymers requires a variety of chemical volatilizing reagents, these chemical reagents may pose risks to both human health and the environment; in addition, these chemicals can potentially residue in the final products, affecting their quality. (3) The structure of nervous organs in human body is very complex, and the damage to the human nervous system involves multiple types of nerve cells, undoubtedly the main problem in the treatment of nervous system diseases. The current electrospinning technology can only simply mimic the neural structure but neglect the neural function, or encapsulate one or more kinds of neurotrophic drugs or neurotrophins; often neglect the functionality, or encapsulate limited neurotrophic compounds. Therefore, the quest to develop electrospinning fibers that closely mimic both the structure and function of nerve tissue may well define the future focus of scientific research in this field.

Here, we summarized the recent progress in the improvement of electrospinning and the electrospinning applications in neurological therapies. Our comprehensive review may serve as a valuable resource to inspire and guide future research endeavors in this promising field.

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CONFLICTS OF INTERESTS

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