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The History of Electrospinning: Past, Present, and Future Developments

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Electrospinning has rapidly progressed over the past few decades as an easy and versatile way to fabricate fibers with diameters ranging from micrometers to tens of nanometers that present unique and intricate morphologies. This has led to the conception of new technologies and diverse methods that exploit the basic electrohydrodynamic phenomena of the electrospinning process, which has in turn led to the invention of novel apparatuses that have reshaped the field. Research on revamping conventional electrospinning has principally focused on achieving three key objectives: upscaling the process while retaining consistent morphological traits, developing 3D nanofibrous macrostructures, and formulating novel fiber configurations. This review introduces an extensive group of diverse electrospinning techniques and presents a comperative study based on the apparatus type and output. Then, each process's advantages and limitations are critically assessed to identify the bona fide practicability and relevance of each technological breakthrough. Finally, the outlook on future developments of advanced electrospinning technologies is outlined, with an emphasis on upscaling, translational research, sustainable manufacturing and prospective solutions to current shortcomings.

1. Introduction

Due to their attractive properties associated with an immense length-to-diameter ratio, the capability of producing smooth nanofibers (NFs), and the ease of manipulating the composition and properties of the fibers formed, electrospinning has been at the cutting edge in the research and industrialization of advanced fiber-based materials.[1,2] Compared to other methods of fabricating fibers within the sub-micrometer/nanoscale, electrospinning is regarded as a scalable, cost-effective, and reasonably automated route of low-labor manufacturing that has continuously gained ground over the past two decades.[3] Electrospun fibers have been widely applied in many fields: tissue engineering,[4–7] drug delivery,[4] sensing,[5] filtration,[10,11] wound dressings,[6,7] self-cleaning surfaces,[8,9] biotechnology,[10] environmental engineering,[11] and green chemistry[12–14] are a few of the many areas in which electrospinning has been explored, among others.

Although conventional electrospinning is a reasonably flexible and straightforward method that can effortlessly produce peculiar fiber morphologies from a range of polymer-solvent systems and complex dopants, including nanomaterials,[15,16] graphene,[17,18] and pharmaceutical compounds,[4] it is unanimously accepted by the scientific

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community that exceeding the associated fiber output limitations is challenging.[19] This is because conventional electrospinning produces a single jet stream deriving from a single Taylor cone during fabrication, thus exhibiting a low yield of ≈0.01–0.3 g h^{-1}.[20] To address this limitation, researchers have devoted considerable effort to resolving this challenge. Notably, between 2004 and 2005, Ding et al.[21] and Theron et al.[22] found a simple way to significantly increase the fiber output by using multiple jet streams instead of a single nozzle. However, this approach proved to be time-consuming and involved a tedious spinneret cleaning cycle to avoid interactions between jets.[3] Later, Dosunmu et al. designed a new type of electrospinning setup using a multi-hole prous cylindrical tube to further increase the output of the process, reaching up to 1 g h^{-1}.[23] However, the porous cylinder spinneret capable of vertically orienting its axis could only deposit fibers in a 360° cylindrical collector surrounding the spinneret, resulting in inconcistent fibrous membranes due to secondary electrical effects and the ease of spinneret clogging.

These issues were resolved by a method developed by Yarin and Zussman in 2004[19] that paved the way for all the high-throughput electrospinning technologies that followed. This method involved the production of free-surface NFs through a two-layer system. By placing a layer of polymer solution underneath a magnetic liquid that overlapped a permanent magnet against a vertically placed oppositely charged magnet by applying high DC voltage, for the first time, jets formed without a needle-based spinneret. A year later, Jiri and co-workers patented a process where a rotating charged electrode, immersed within a polymer solution, placed at a close distance to a counter electrode in a bottom-up position, could be used to fabricate NFs at an increased production rate with the assistance of an airstream to increase the auxiliary drying efficiency of the system.[24] Gradually, more needleless electrospinning methods were reported, further improving the productivity and quality of the fibers with the primary purpose of achieving industrial-scale NF production.

This comprehensive review critically discusses the history and evolution of electrospinning technology. A detailed introduction to the most used electrospinning techniques is succeeded by a comparative study focusing on the advantages and disadvantages of each method. Thereafter, the limitations of the different techniques are discussed, followed by an outlook on the future of advanced electrospinning technologies.

2. Brief History

A lengthy chronology of inventions and innovations accompanies the history and progress of electrospinning. Electrospinning is the descendant of electrospraying, a conceptually similar technology that employs electric forces to disperse a liquid or fine aerosols out of a polymer solution, first carried out in 1747 by Abbé Nollet[25] and first patented by John Cooley[26] and William Morton[27] in the early 1900s. When electrospinning, a fluid withdrawn through the spinneret is electrically charged, acquiring a nearly conical shape from the apex of which a jet arises.[28] In 1914, John Zeleny first demonstrated that the jet ejection at the tip of the metal capillary presents a liquid drop surface tension held at the edge that disintegrates onto a spray as the voltage increases.[29] Later, the earliest method of producing nanofibrous materials from polymer solutions was patented by Anton Formhals in 1934.[30] Between 1964 and 1969, Geoffrey Taylor, appertaining to Zeleny's work, mathematically demonstrated that the critical half-angle of the meniscus nears 49.3° at the furthest point before the disintegration event, illustrating why a polymer solution or melt extruded through a capillary will reshape from a spherical to a conical configuration in a strong electric field.[31,32] This gave rise to the concept of the "Taylor cone" formation. However, no significant electrospinning developments were reported in the literature in the following two decades. This loss of attention from academia and industry coincides with the lack of accurate methods to observe the morphology and measure the diameter of fibers down to the sub-micrometer scale.

It was not until the early 1990s, due to the increasing interest in nanotechnology, that the study of electrospinning technology started to gain popularity.[33] The modern era of electrospinning began with work conducted by Jayesh Doshi and Darrell Reneker,[34] who reported that the diameter of the fibers is inverse proportional to the distance from the needle tip to the collector. From 1999 to 2001, Reneker and Gregory Rutledge worked to better understand the parameters influencing the electrospinning process,[35,36] owing to the advancement of scanning electron microscopy (SEM) that enabled fibers within the nanometer scale to be observed in detail. These advancements commended the capabilities of electrospinning to the scientific community for the first time.

As depicted in **Figure 1**, electrospinning has gained significant attention since the turn of the century, with a consistent exponential increase in the number of published works in the field. Studies surrounding the working electrospinning parameters and understanding how different polymers can be processed into fibers flourished. This was followed by research groups developing novel electrospinning apparatuses, including co-axial, tri-axial, centrifugal, corona, bubble, rotary metals (cylinder, disk, ball), high-speed, and 3D electrospinning (**Table 1**), which are expounded in this review. These advanced techniques have expanded the range of materials that can be used to fabricate fibers and the gamut of obtainable structures. The main principles behind developing these apparatuses has been to improve the fiber output and the fibers' macro and microarchitecture, further widening the reach of electrospun materials.

3. Background and Classification

3.1. Principles and Process Parameters

Among the processing techniques, including thermal-induced phase separation, drawing, template synthesis, and self-assembly, electrospinning is of considerable significance as a rapidly evolving fiber preparation method.[52] This highly versatile method is used to process solutions, suspensions, or melts into continuous fibers of nano/microscale diameters[53] and is the only method capable of mass-producing continuous fibers at this range.[54]

Electrospinning is one of the most conventional methods used for continuous fiber preparation today and is based on the principle that electrostatic forces can be used to form and expand fibers out of a polymer solution.[55] As expounded in the previous section, the principle of this process was first described in the 1930s in a patent entitled "Process and Apparatus for

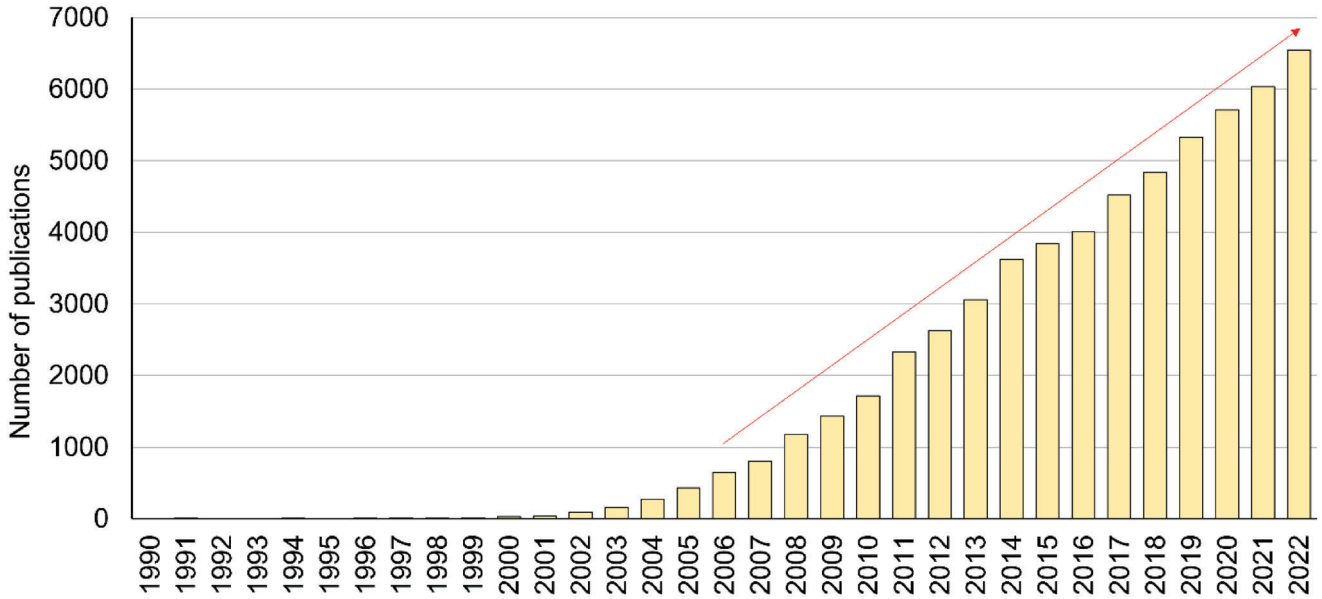

Figure 1. Progress in electrospinning research based on publication output over the years. Data obtained from Scopus (Elsevier) based on the searching command "TITLE-ABS-KEY electrospinning OR electrospun OR electrospin* AND LIMIT-TO (DOCTYPE , "ar")".

Table 1. Milestones in the development of electrospinning methods.

Electrospinning methods	Year	Inventor	References
Mono-axial	1902	Cooley and Morton	[26,27]
Co-axial	2003	Sun et al.	[37]
Multijet	2004	Ding et al.	[21]
Magnetic fluid	2004	Yarin et al.	[19]
Roller	2005	Jirsak et al.	[24]
Centrifugal	2006	Andrady et al.	[38]
Porous tube	2006	Dosunmu et al.	[23]
Bubble	2008	Liu et al.	[39]
Tri-axial	2009	Kalra et al.	[40]
Conical wire coil	2009	Wang et al.	[41]
Ball	2009	Miloh et al.	[42]
Disk	2009	Niu et al.	[43]
Wet (3D)	2009	Yokoyama et al.	[44]
Cone	2010	Lu et al.	[3]
Spiral coil	2012	Wang et al.	[45]
Corona	2012	Molnár et al.	[46]
Stepped pyramid	2013	Jiang et al.	[47]
Beaded chain	2014	Liu et al.	[48]
High-speed	2015	Nagy et al.	[49]
Cold-plate (3D)	2015	Sheikh et al.	[50]
Three-dimensional (3D)	2018	Vong et al.	[51]

Preparing Artificial Threads" by Anton Formhals, considered the father of electrospinning.[56] However, considerable emphasis was not given to the process until the 1990s in works led by Reneker and Rutledge, who described the process.[34]

The electrospinning process is related to an electrohydrodynamic problem. It is a simple and cost-effective method that uses electrostatic forces to produce and expand fibers from polymer solutions or melts with diameters ranging from a few tens of nanometers to micrometers.[55] During electrospinning, high voltage is applied to charge a liquid solution or melt by placing it between two conductors that endure the electromagnetic charge of opposite polarities, stretching the polymer to form fibers.[57] A standard laboratory-scale setup consists of four main components: a high-voltage DC (or AC) power supply, a syringe pump, a nozzle (usually a metallic capillary), and a collector (which can be a metallic foil, plate, or disc). The electrostatic force produced by the high-voltage supply is applied to the polymer solution or melt, which is dispensed through the fine needle orifice at a controlled rate. When electrospinning, the precursor solution extruded from the spinneret orifice forms a small droplet that is subject to an accumulated charge in the presence of an electric field.[58] The electric discharged of the polymer droplet, induces a conically-shaped geometry referred to as the Taylor cone.[59,60] Increasing the strength of the electric field causes an increased accumulation of charges at the surface of the polymer bud. After this, the repulsive electric forces overcome the surface tension of the polymer solution or melt, leading to vigorous whipping and splitting motions due to the bending instabilities generated, causing the fiber to elongate through the application of mechanical force.[61] At this point, the geometry of the formed asymmetrically electrospun (as-spun) fibers is directed by the electrostatic repulsion, colloid stability, the incoming surface ratio, and gravity.[55,57] The solidification of the liquid solution occurs by establishing a zone that thrusts the charged molecules, allowing for continuous solvent evaporation, stretching the drawn polymer threads as they advance toward the grounded or oppositely charged collector.[55] This transition between the liquid and solid phase is due to the Ohmic current primarily being transited to convective flow, thus increasing its acceleration.[62] **Figure 2** illustrates the basic concept behind the electrospinning process.

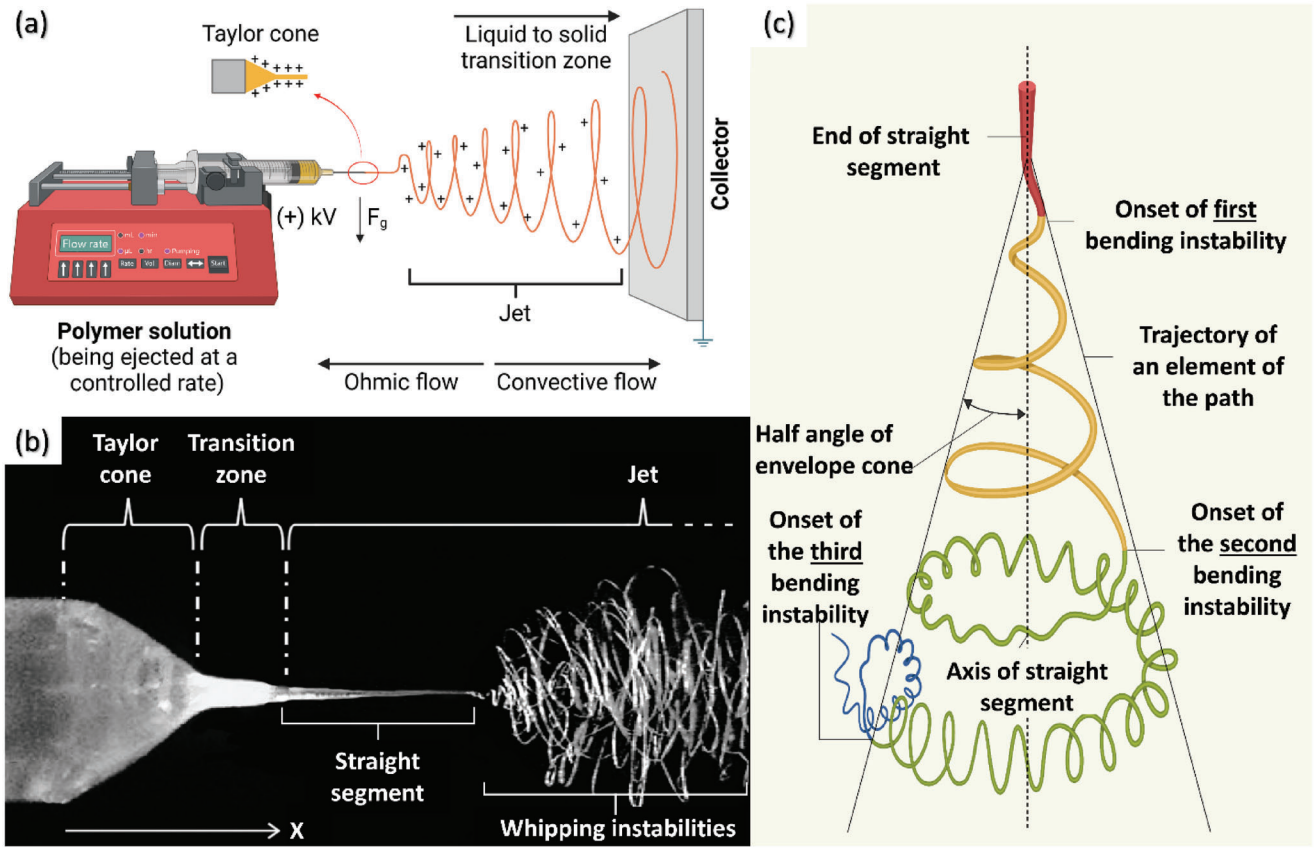

Figure 2. Fundamentals of electrospinning. a) Schematic representation of the electrospinning concept (created with Biorender); b) high-speed photograph outlining the Taylor cone formation, depicting the linear segment of the polymer jet, followed by the whipping jet region, modified from refs. [63] and [64]; c) the prototypical instantaneous position of the jet path succeeding through the three sequential bending instabilities, modified from ref. [58], Copyrights: (a) created with BioRender; (b) Adapted (right segment) with permission.[63] Copyright 2013, AIP Publishing; (b) Adapted (left segment) with permission.[64] Copyright 2007, Elsevier; (c) Adapted with permission.[58] Copyright 2019, American Chemical Society.

The formed electrospun mats exhibit a web-like fibrous structure due to the considerable extent of plastic deformation caused by the high charge density of the jet and the unstable whipping motion.[65] This phenomenon is known as bending instability, and it leads to randomly oriented and nonaligned fibrous mats.[66]

NFs carry a range of novel physical and chemical properties that are not present in their corresponding macroscales, resulting in many characteristics shared among materials at the nanoscale.[67] Due to high specific surface area, a large surface-to-volume ratio, and an extensive fiber length-to-diameter aspect ratio, properties such as peculiar quantum effects, electrical conductivity, redox potential, and the formation of crystal and magnetic structures increase their reaction rates per given mass.[65] Moreover, those properties allow the construction of highly porous constructs with adjustable pore size and wide surfaces that allow chemical functionalization.[65]

Through the continuous research and evolvement of these basic principles and the manipulation of the conventional electrospinning apparatus, unique morphologies and structures have been successfully produced over the past two decades, as indicated in the examples presented in **Figure 3**.

The parameters influencing the electrospinning process[77] can be classified based on solution and solvent, operating, and ambient conditions (**Figure 4**). Solution parameters refer to polymer concentration and polymer molecular weight, solvent volatility, solution viscosity, surface tension, and solution conductivity, among others. Concerning the electrospinning parameters, the electric field strength, electrostatic potential, flow rate, and distance between the spinneret and the collector must be appropriately adjusted in conjunction with the polymer solution properties. Finally, ambient parameters refer to the chamber and solution temperature, humidity, and type of atmosphere, among others.

In general, by prolonging the fiber elongation or flight time during the electrospinning process, finer fibers can be produced, which can be achieved by increasing the distance between the collector and the spinneret. Moreover, the evaporation rate of the solvent can be increased by using low-volatility solvents and raising the chamber temperature. However, it must be noted that increasing the working distance beyond the critical threshold (the point at which the stability of the Taylor cone is impaired) results in a significantly longer flight time, which can lead to inhomogeneous fiber formation.[4] Insufficient solvent volatility and

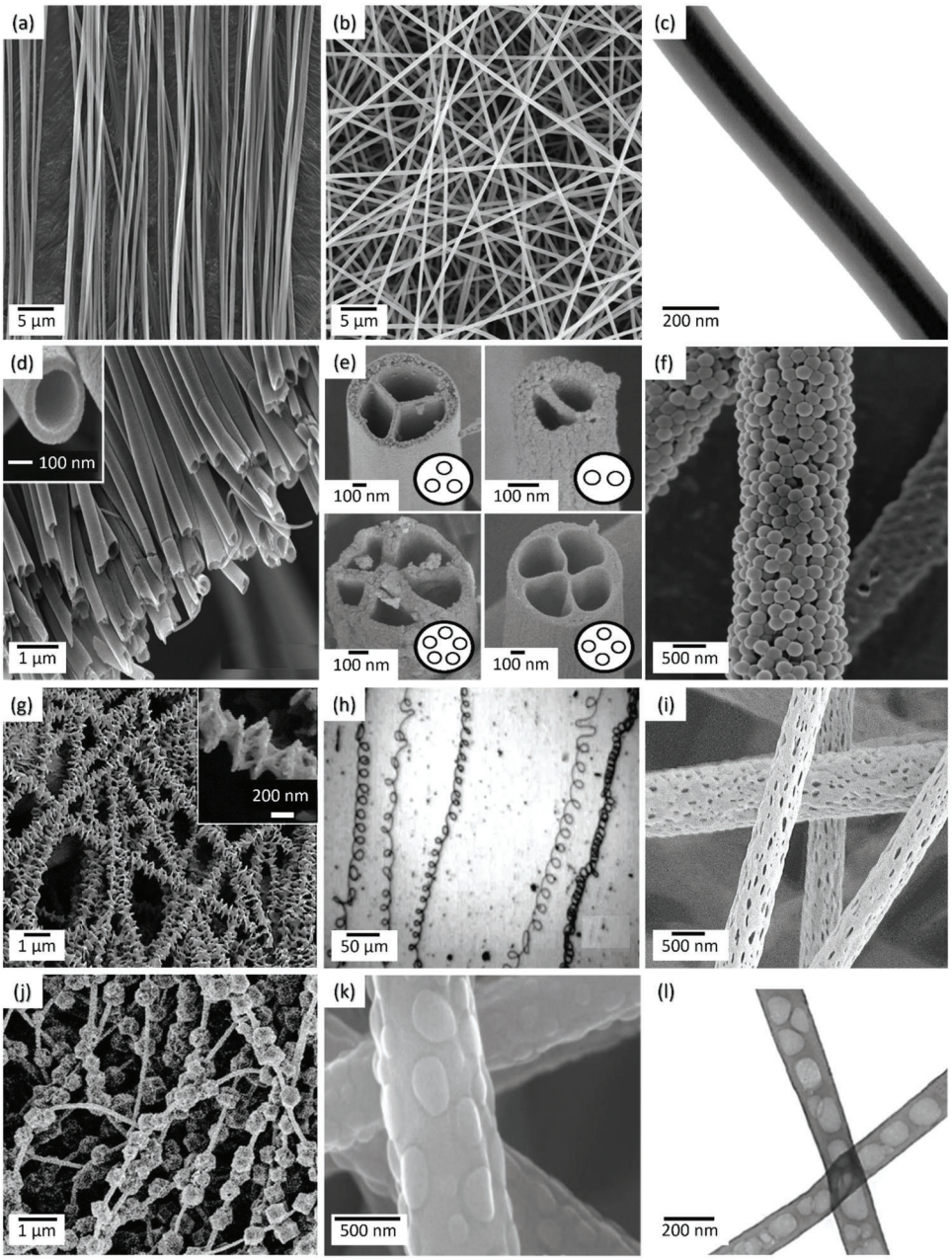

Figure 3. Structural diversity of individual electrospun fiber morphologies: a) aligned; b) randomly oriented; c) core/shell;[68] d) hollow;[68] e) multichannel microtubes;[69] f) colloidal nanoparticle-decorated;[70] g) shish-kebab;[71] h) helical;[72] i) porous; j) necklace-like;[73] k) island-like;[74] l) beads-in-fiber,[75] electrospun fibers. Copyrights: (c, d) Reproduced with permission.[68] Copyright 2004, American Chemical Society; (e) Reproduced with permission.[69] Copyright 2007, American Chemical Society; (f) Reproduced with permission.[70] Copyright 2013, American Chemical Society; (g) Reproduced with permission.[71] Copyright 2021, Royal Society of Chemistry; (h) Reproduced with permission.[72] Copyright 2012, American Chemical Society; (i) Produced from author A.K. (j) Reproduced with permission.[73] Copyright 2008, Elsevier; (k) Reproduced with permission.[74] Copyright 2017, American Chemical Society; (l) Reproduced with permission.[75] Copyright 2020, Springer Nature.

low temperatures may lead to wet fiber fusion during deposition. Therefore, the parameters that affect the electrospinning process must be observed and monitored to determine the ideal operating conditions that can yield optimized fiber characteristics tailored to the specific requirements of each study.

One of the most important parameters for obtaining an electrospinnable solution is determining the chain entanglement of the polymer solution from the molecular weight and its concentration. Within a solution, the root-mean-square distance of the segment of a molecular chain toward the center of its mass provides the average radius of gyration (R_g).[76] If the concentration is too low (diluted solutions), the polymer chains do not overlap, with the viscoelasticity of the solution being governed by shorter polymer chains. When the concentration of the polymer is in-

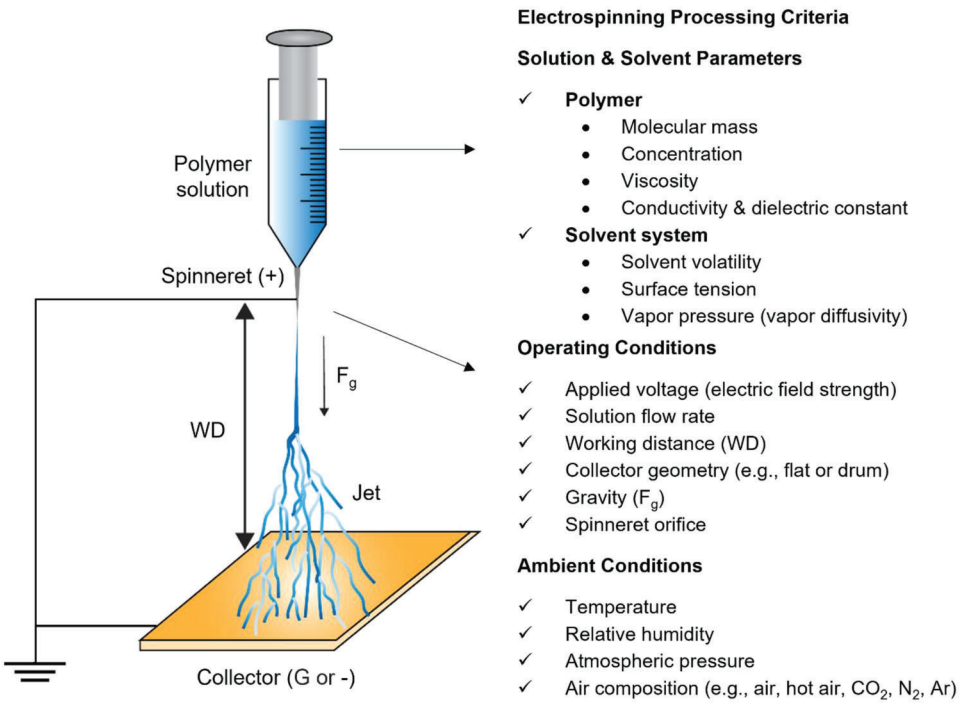

Figure 4. Schematic representation of the electrospinning processing parameters. Several criteria must function concurrently under optimal conditions to attain a stable electrospinning process. These can be classified based on solution, operating, and ambient parameters. These conditions are further responsible for the process's production rate, physicochemical characteristics, and morphological properties.

creased, entanglement occurs as the polymeric chain begins to overlap.

The critical concentration (C_c*) is generally accepted to be proportional to the polymer's molecular weight (M_w) and the effective solvent volume

$$C_c^* = \frac{3M_w}{4\pi R_g^3 N_A} \quad (1)$$

where N_A is the Avogadro constant.[77] If the polymer concentration is below the critical point ($C < C_c$*), inadequate chain entanglement can result in an unstable jet due to Rayleigh instabilities. Therefore, for stable electrospinning, the polymer concentration needs to be higher than the critical point ($C < C_c$*).[78] In many cases, the correlation between the M_w of a polymer solution and its corresponding R_g value is evident. Thus, in some instances, attempting to electrospin variant molecular weights of the same polymer can ultimately contribute to the procurement of the required concentration (beyond C_c*) for effective and stable electrospinning.

Selecting the ideal operating range of each electrospinning condition can be challenging when designing an experiment, due to the vast choice of polymers and the corresponding solvent systems. Moreover, most parameters are interdependent, leading to nonlinear causality, one of the significant challenges in the electrospinning field. Understanding the parameters that influence the electrospinnability of a polymer solution and the subsequent properties of the fibers formed has made it possible to advance polymer chemistry and evolve the capabilities of the produced electrospun scaffolds. Though the majority of present research surrounds the use of the conventional needle-based setup with either a drum or a flat collector, significant research has focused on further manipulating the design of electrospinning devices based on the fundamental principles described in this section, to further advance the producibility and morphological architecture of the fibers. For instance, co-axial and multi-axial electrospinning apparatuses can produce fibers from highly diverse polymer pairs, e.g., core–sheath, hollow, and nanoparticle-decorated, while each one can maintain its separate material identity. A high fiber production rate can be achieved by increasing the surface area of the spinneret via technologies such as free-surface and needleless electrospinning. 3D buildups can be conveyed by incorporating 3D printing and electrospinning, whereas ultrathin-aligned NFs are obtainable via centrifugal electrospinning. Finally, portable electrospinning apparatuses have been developed for biomedical applications, where fibers can be directly deposited into an open wound. As described in the following sections, advances in such apparatuses have managed to keep electrospinning on the frontline of research.

3.2. Instrumentation

Despite the apparatus's design and configuration, the electrospinning process will always consist of three main components: a high-voltage power supply, a jet generator, and a collector.

When high-voltage power is applied to the spinneret, a strong electric field is created around a pendant droplet. This causes the droplet to overcome surface tension and, in the presence of suffi-

cient molecular cohesion, commences jetting. The jet is directed by the movement of charged molecules from high to low voltage.

The jet generator, commonly referred to as the spinneret, introduces the polymer solution into the electric field and facilitates liquid distortion, Taylor cone formation, and jetting. The spinneret is the principal component differing between needle-based and needleless methods. In nozzle-based methods, the spinneret can be monopolar or consist of multineedle concentric arrangements. In the case of needleless methods, the spinneret configuration can vary significantly in form, with structures such as wire, corona, cylinder, ball, and bubble, among others.

Finally, the collector, either grounded or charged oppositely to the spinneret, directs the travel path of the jet, allowing for the fibers to be deposited while discharging them at the collector's surface. Although the collector's configuration does not play a significant role in the fiber production rate, it can influence fiber morphology and is responsible for the dimensions of the electrospun membranes produced. Traditionally, a metallic plate is used to produce randomly-oriented fiber mats, while a solid cylinder at high revolutions per minute can introduce fiber alignment. Nonetheless, variant collectors have been reported in the literature, including roller, rotating wire drum, knife-edged, honeycomb, and liquid bath, among others, capable of generating complex fiber morphologies.[79,80] Industrial-size, commercial-scale electrospinning units can provide continuous production lines by depositing fibers in a supporting textile using a feed/take-up dual cylinder system. This can significantly increase the output and dimensions of the produced materials to anywhere between 10 and 800 sq m h^{-1} and 0.01 and 2 g m^{-2}, respectively. For instance, a thicker deposition will coincide with a smaller membrane/fabric area; on this account, determining the solid content when measuring the output can be a better indicator.

3.3. Solvent Selection

Although it is feassible to procure electrospun fibers via solvent-free techniques, such as melt electrospinning and melt blowing, the higher temperature required to melt the polymer during processing can lead to thermal degradation, which limits the materials that can be electrospun (e.g., small molecules, nanomaterials, and bioactive compounds).[14] Moreover, melt spun fibers tend to have langer diameters, primarily due to the much higher viscosity of polymer melts and poorer conductivity. Most of the research conducted on electrospinning relies on solvent-based methods, due to the greater flexibility, fewer limitations and the greater number of available technologies.

As described, in detail, in **Table 2**, at the end of the section, the polymer solution parameters are interdependent. For solution electrospinning, a solvent must be able to solubilize the polymer homogeneously while sufficiently evaporating during jetting, inducing fiber solidification. The choice of solvent has a substantial impact on solution spinnability and the fiber morphology. Experimentally, solvent selection is generally conducted by determining the chemical structure and properties of the polymer, establishing a list of compatible solvents; based on their physical properties, and conducting short parametric studies focused on solubilization and electrospinnability. Mathematically, the Hansen solubility parameter can be used to estimate the solvent's ability to interact with the polymer chains, taking into account the energy from the dispersion forces, the dipolar intermolecular force and hydrogen bonds.[77] Based on the selected solvent system, as described in the previous section, determining the critical concentration can be advantageous. This can influence processing stability by determining the necessary minimum solution concentration. Higher molecular weight polymers are more resistant to solvent dissolution and may require the application of heat below the polymer's melting point, in order to avoid polymer degradation, while promoting solubilization.

As a great number of parameters need to be met by a solvent to induce stable jetting, it is a common practice to use solvent-systems; mixtures consisting of two or more compatible solvents. In the realm of electrospinning, the most frequently utilized solvents are halogenated solvents (e.g., chloroform, trifluoroethanol), tetrahydrofuran (THF), aprotic solvents (e.g., dimethylformamide [DMF], dimethylacetamide [DMAc], dimethyl sulfoxide [DMSO]), and protic solvents (e.g., ethanol, acetone, water).[14,81] Halogenated solvents remain at the forefront of lab-scale electrospinning research due to their high rates of hydrophobic polymer dissolution and low boiling point, which is of special interest to polymers resistant to many standard organic solvents, such as fluoropolymers.[82]

As the electrospinning process moves towards upscaling technologies, larger amounts of solvents for fiber processing, which has led to the investigation of green and sustainable solvents. This coincides with regulatory agencies, such as the Chemical Control Regulation in the European Union (REACH), setting the rationale and strict limitations on the use of harmful solvents (such as DMF, toluene, chloroform, and dichloromethane) to prevent workplace exposure and environmental contamination risks.[85] Along with the environmental impact and user safety, the selection of green(er) solvents should also consider production sustainability (e.g., emissions, energy efficient, whether it can be sourced from renewable sources), solvent recyclability, and disposal.[86] An overview of several studies that have focused on substituting harmful conventional solvents for green alternative is provided in **Table 3**. As a relatively new area of interest in response to society's growing enviromental consciousness and focus on sustainability, green chemistry focused on electrospinning is a critical research question that has yet to be fully explored.

3.4. Materials Selection

The most prevalent research question that has propelled the advancement of the field has been answering, "what can be electrospun?". This has given rise to a wide range of common and intricate materials being successfully electrospun into fibers. Although principally, electrospinning relies on polymeric materials, ceramics, metals, and inorganic chemical compounds can also be transformed into fibers in the presence of a carrier polymer, which can be subsequently kept or removed through postfabrication processing. In addition, small molecules can be electrospun by tuning their chemistry to attain sufficient polymer chain entanglement or by incorporating a readily electrospinnable high molecular weight carrier polymer. As a broad clas-

Table 2. A detailed account of the solution, operating, and ambient parameters influencing the electrospinning process and fiber formation.

Parameters		Influence on electrospinning
Solution parameters	Molecular weight	– The length of the polymer chains has a direct effect in facilitating or obstructing chain extensibility. – Sufficient topological entanglements coupled with an appropriate solvent system are required. – Generally, higher molecular mass polymers are associated with more uniform but thicker fibers. While insufficient molecular mass will either hinder electrospinning or produce non-uniform fiber mats.
	Concentration	– Composite blends generally produce larger fibers due to a denser polymer entanglement. – Increasing the polymer concentration is associated with uniform and more elongated fibers with no or fewer secondary morphologies (e.g., beads and spider webs) and a smaller fiber diameter standard deviation. – Low concentrations inhibit fiber formation due to inadequate surface tension, causing jet fragmentation.
	Viscosity	– Viscosity increases as intermolecular interactions and/or molecular weight increase. – Viscosity is dependent on the shear rate and temperature. – Attaining appropriate viscosity during electrospinning can prevent polymer spraying (low) or the formation of large-diameter fibers (high).
	General note	– Viscosity, molecular weight (M_w), and concentration are intertwined. The average number of entanglements per chain increases with M_w, whereas the entanglements per mass/volume increase with concentration.[83]
	Surface tension	– Surface tension is responsible for instigating the electrohydrodynamic events of the electrospinning process. – Surface tension is associated with a liquid surface taking up the minimum surface area required (the force required from a specific mass along a line of unit length). – The electric field required to initiate electrospinning correlates to the surface tension, which, in turn, will depend on the spinneret's configuration. – As the surface tension increases, a stronger electric field is needed to commence electrospinning. This can sometimes be adjusted during electrospinning, e.g., beginning with higher voltage and lowering it after a stable jet has formed. – Surfactants can enhance electrospinnability by improving polymer spreading and/or increasing the solution's conductivity (especially for needleless spinnerets). – Needleless electrospinning techniques require a higher voltage because of the higher surface tension that must be devolved to instigate jet formation.
	Conductivity and permittivity	– Two electrostatic forces set in motion, Taylor cone formation and jetting; electrostatic repulsion between the surface charges and a Coulombic force applied by the external electric field.[84] – An appropriate solution conductivity increases the number of charges that can be carried out while reducing the minimum voltage required for jet eruption. – Although theoretically, the fiber diameter decreases with increased solution conductivity, by promoting polymer stretching, in practice, a too-high conductivity will produce unstable jetting due to electrical air discharges. – Permittivity refers to the proportion of electric displacement toward the intensity of the electric field. Reducing the solution's permittivity can increase the electric field intensity. – When insufficient, introducing small amounts of salt (e.g., NaCl, LiCl, tetraethylammonium bromide [TEAB]) in the polymer solution can significantly increase the conductivity and permittivity. This approach is commonly used in needleless electrospinning to increase fiber output by increasing the number of formed Taylor cones.
Solvent parameters	Solvent volatility and vapor pressure	– During electrospinning, fiber solidification relies on the solvent system's evaporation rate, and thus the volatility of the selected solvent system can influence the morphology of the fibers. – An adequate evaporation rate will allow the collection of dry membranes, while reducing the degree of solvent entrapment. – A too-volatile solution can induce morphological traits/defects (e.g., porous fibers in the presence of a non-water-soluble polymer) or even hinder electrospinning. – Vapor pressure can promote further solvent evaporation, generating noncylindrical secondary morphologies, such as spider webs. – A commonly used term in electrospinning, evaporation rate, will rely on a combination of parameters being met alongside the solvent's volatility, including relative humidity, working distance, and spinneret configuration.
	Dielectric constant	– The dielectric constant refers to the solvent's capability to retain the electrostatic repulsions induced by the electric charge affecting the surface charge distribution. – A higher dielectric constant will improve surface charge distribution and jet stability. For instance, water presents a high dielectric constant that can weaken the electrostatic repulsions and is, thus, commonly incorporated as part of solvent systems.

(*Continued*)

Table 2. (Continued).

Parameters		Influence on electrospinning
Operating conditions	General note	– The operating condition requirements will differ greatly between needle-based and needleless electrospinning technologies.
	Applied voltage	– As an electrohydrodynamic process, electrospinning relies on applying high voltage to a polymer solution to initiate the process. – A minimum threshold voltage influenced by the surface tension of the polymeric solution, referred to as critical voltage, V_K, must be surpassed for jet generation. – Increasing the voltage above the required threshold generally reduces the jet's "flight time," producing an unstable jet path with larger diameter fibers or secondary fiber morphologies. – A voltage below the required threshold will, in most instances, spray the polymer solution onto the collector or along the jet path. – Needleless electrospinning technologies require a substantially higher V_k due to the greater surface tension.
	Solution feed (flow) rate	– The flow rate, which is the amount of solution exposed to the high electric field at a given time, is the main contributor affecting surface tension and the $V_{K.}$ – The effect of the solution feed rate will be directly influenced by most of the parameters discussed in this table. Increasing the flow rate will generally promote insufficient fiber stretching, which can produce wet or thicker fibers with larger pores. – Flow rate plays a key role in multi-axial needle-based electrospinning. – Although, as a term, "flow rate" is not typically used in needleless electrospinning, the way that the solution is introduced into the needleless spinneret (e.g., via cartilage, a solution bath, among others) can positively or negatively affect the homogeneity of the produced fibrous membranes.
	Working distance	– Working distance refers to the distance between the spinneret and the collector, which defines the jet path. – Increasing the working distance can give more time for a less-volatile solvent to evaporate and for the polymer to solidify. Expanding the jet path is also associated with thinner fibers and vice versa. – Exceeding the critical distance can halt electrospinning or produce defective fibers due to prolongated bending instabilities, affecting fiber branching
	Collector geometry	– The collector's geometry can directly affect the micro and macromorphological properties of the deposited fibers. – A collector can provide alignment (e.g., a rotating mandrel), orientation (e.g., a cylindrical collector surrounding a rotating spinneret), facile patterning (e.g., honeycomb mesh), and mass production (e.g., supporting textile dual cylinder system).
	Spinneret design	– The spinneret type is the cardinal difference between needle-based and needleless electrospinning and the principal focus of this review. – The spinneret configuration will affect the output of each technology, the complexity and architecture of the developed fibers (e.g., co-axial), and even the properties of the developed constructs (e.g., 3D macrostructures or alignment due to a rotating spinneret).
Ambient conditions	Temperature	– The chamber temperature during electrospinning will affect the solution viscosity and surface tension, the solvent's evaporation rate, and the jet solidification rate. – Depending on the polymer and solvent-system properties, the working temperature can positively and negatively affect the process.
	Relative humidity	– High relative humidity can induce non-uniformity, and in the case of hygroscopic polymers, unique fiber configurations (such as porous, dimpled, or pitted fibers) when other solution parameters are sufficiently met. – High humidity can also hinder electrospinning by affecting the total charge distribution and reducing the surface charge density. – Due to rapid solvent evaporation, very low humidity can reduce the flying jet path, producing thicker fibers.

sification, these can be divided into three principal groups: organic polymers, small molecules, and composite materials.

3.4.1. Organic Polymers

Organic polymers in the form of solutions or melts are the most frequent employed materials in electrospinning. In recent years, over two hundred polymers have been successfully fabricated into fibers and applied in various fields.[100] Based on their occurrence, an extensive number of natural, synthetic, and semisynthetic polymers have been manipulated into electrospun fibers. Polymers of all forms; homopolymers, copolymers, and blends can produce stable electrospinning solutions. Unlike copolymers where covalent bonding is present, blended polymers are created by physical mixing of two or more polymers. Copolymers and polymer blends are readily employed to attain hybrid physicochemical and mechanical properties. Although consistency and reproducibility among batches to produce homogenous fibers of desired morphology will require optimization of the

Table 3. Overview of recent studies utilizing green, environmentally safe, and biorenewable solvents for electrospinning.

Solvent system	Polymer (additives)	Electrospinning technique	Ref.
2-Methyltetrahydrofuran (2MeTHF)/formic acid	Poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate (PHBV)	Mono-axial (using a syringe heater, to prevent sol-gel transition)	[87]
Acetic acid/ethyl acetate/water	Polycaprolactone (PCL) + gelatin	Mono-axial (blend)	[88]
Acetic acid/formic acid/acetone	PCL	Needleless (AC)	[89]
Acetic acid/water	Cellulose acetate (CA) and chitosan (CS)	Co-axial electrospinning	[90]
Ethanol	Ethanol-soluble polyurethane (TPU) and thymol (antibacterial compound)	In situ (handheld)	[91]
Ethanol	Polyvinylpyrrolidone (PVP)	Needleless (wire)	[92]
Ethanol/diacetone alcohol	Polydimethylsiloxane (PDMS) and polyamide pellets	Mono-axial	[93]
Ethanol/water	Chitin propionate and PEO	Mono-axial (blend)	[94]
Ethyl acetate/acetic acid	Ethylcellulose polyglycerol polyricinoleate (surfactant) + polyethylene glycol (PEG)	Mono-axial (emulsion)	[95]
Dimethyl carbonate (DMC)/water	Polylactic acid (PVAc) + tetrabutylammonium bromide (TBAB, salt)	Mono-axial	[96]
Dimethyl sulfoxide (DMSO)/acetone	Polyacrylonitrile (PAN)	Centrifugal	[97]
DMSO/acetone	Polyvinylidene fluoride (PVDF) + LiCl (additive salt)	Mono-axial	[98]
Methyl ethyl ketone (MEK)/formic acid	PHBV	Mono-axial (using a syringe heater, to prevent sol-gel transition)	[87]
Water	Polyethylene oxide (PEO)	Needleless ultrasound-enhanced electrospinning (USES)	[99]

parameters mentioned above, in concept, the predominate number of organic polymers can be electrospun in the presence of a suitable solvent (for polymer solutions) or by obtaining melts without thermal degradation (for polymer melts).

The nature of the polymer will have a direct effect on the properties of the fibers. Selecting the appropriate polymer for the application of interest is an indispensable step. Synthetic polymers for electrospinning are generally chosen based on thermal behavior and molecular force properties with thermoplastics (e.g., polyesters, polystyrene [PS], polyvinylidene fluoride [PVDF], nylon-6, among others), thermosets (e.g., polyurethane [PU], polymethyl methacrylate [PMMA], among others) and elastomers (e.g., polyurethane [PU], polyglycerol sebacate [PGS], among others), all readily electrospun. For biomedical applications, biopolymers are classified based on their origin to natural (e.g., proteins,[101] nucleic acids,[102] and even polysaccharides[103]) and synthetic, which can be subcategorized into non-biodegradable (e.g., polyvinyl chloride [PVC], polypropylene [PP], among others) and degradable (e.g., polycaprolactone [PCL], polylactic acid [PLA], poly(ethylene oxide) [PEO], polyvinylpyrrolidone [PVP], among others). Aliphatic polyesters intrinsically conductive polymers (ICPs) have also been successfully electrospun to develop flexible electronics, conductive coatings, energy nanogenerators, supercapacitors, batteries, and biosensors.[104] ICPs like polypyrrole (PPy), poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS), and polyaniline (PANI), have been electrospun in the presence of carrier polymers, as blends. In the case of ICPs, incorporating a carrier polymer is generally considered a *sine qua non* to improve the low molecular weight, high molecular chain rigidity, and poor solubilities associated with the ICPs. At the same time, the increased solution conductivity can overly increase the level of charge distribution, facilitating jet instability.

3.4.2. Small Molecules

Chain entanglement can control molecular motion and disrupt the free movement of molecular segments, thus influencing a polymer's rheological, morphological, and mechanical properties. Increasing the degree of chain entanglement can reduce the effect of Rayleigh's instabilities and maintain a stable jet.[105] Thus, under the appropriate conditions, small molecules that can self-assemble in the presence of the appropriate solution conditions (for instance, through anionic or non-anionic noncovalent bonding) may attain sufficient chain entanglement to be electrospun into fibers. In addition, the self-assembled structures of molecules can be stable in solutions or melts when adequate intramolecular interactions form. Among the small molecules successfully electrospun are phospholipid amphiphiles, monopeptides, dipeptides, tetraphenylporphyrin compounds, and cyclodextrins.[106–109] In instances where a small molecule cannot produce stable intramolecular interaction to obtain the required chain entanglement, carrier polymers may be incorporated into the polymer mixture and subsequently removed through postfabrication strategies (e.g., solvent or heat treatment). Another way that small molecules can be manipulated into fibers is through in situ polymerization approaches, such as photopolymerization.[110]

3.4.3. Composite Materials

Many state-of-the-art fibrous materials are forged from composite polymer blends based on sol-gel chemistry principles. While polymer–polymer composites, where polymers of differing physicochemical characteristics can produce peculiar composite fibers that bring together their distinct properties (such as, adjustable biodegradability and biocompatibility along with mechanical stability), incorporating colloids in a polymeric solution can be implemented to immobilize nanomaterials within the fiber configuration. Colloids are good examples of polymer-particle composite electrospun structures that rely on the particles' aggregation state within a solution during electrospinning. A stable jet can be maintained when sufficient polymer entanglement and particle distribution are present, allowing composite fibers to form.[58] To produce electrospinnable solutions consisting of polymer–colloid systems, in general, a less viscous solution of lower concentration and higher molecular weight, along a compatible solvent system of lower conductivity, to account for the addition of the desirable compound, is required. Typically, the material is first dispersed in a polymer-compatible solvent and homogenized trough ultrasonication before being introduced into the polymeric mixture and vigorously stirred. The morphology of the composite fibers will be affected by the critical value of the average particle diameter and its impact on the polymer solution's properties, such as conductivity and viscosity. Through this process, a variety of materials and substances can be successfully incorporated into a fiber configuration, including carbon, organic and inorganic 0D, 1D, 2D, and 3D nanostructured materials, as well as pharmaceutical compounds. Table 2 provides a comprehensive list of the parameters that need to be met for consistent electrospinning and homogeneous fiber formation.

Although significant efforts have been directed towards achieving intricate fibrous membrane properties by manipulating the produced membranes during electrospinning (e.g., a coagulation or oxidizing bath collector), or post-fabrication (physical or chemical), including surface modification (e.g., grafting), in situ polymerization, plasma treatment, carbonization, physical vapor deposition, sputter coating, electrospraying, among other, the subsequent sections of this review will exclusively focus on apparatus-specific technological advancements.

3.5. Predictive Modeling

As a critical design tool, modeling and simulation (M&S) has played a tremendous role in understanding the complex interdependent events that collectively make electrospinning feasible. Prediction models, where experimental work falls short, can provide important insights about the underlying processes, as well as reduce unnecessary trial-and-error experimentation, thus saving resources (e.g., significantly reducing the use of solvents). Today's understanding of the polymer solution properties, external forces affecting the electrospinning process, as well as the formation stages; Taylor cone, jetting, elongation, jet instability, and solidification, would not have been possible without the collective efforts of several research groups providing those mathematical models.[111]

In recent years, M&S has focused on improving the consistency of the process and the likelihood of attaining invariable fiber morphological traits, as well as understanding the electric field intensity and distribution based on spinneret configuration (e.g., needleless cylindrical systems) and collector shape.[112]

A technological constraint that continues to exist today is having physical control over the fiber diameter and attaining a low standard deviation. Although empirical findings can determine to a great extent, variations in fiber diameter based on solution composition and electrospinning properties, to date, there is no library encompassing the extensive experimental work that has been carried out in the field over the years. Taking advantage of the vast number of trial-and-error studies conducted, M&S, could ultimately provide an accurate, predictive tool utilizing a verified model that considers the wide range of experimental parameters.

The response surface methodology (RSM) is a statistical polynomial method that explores the relationships of several explanatory and response variables to demonstrate and analyze existing relationships. RSM aims to optimize the response of output variables by influencing the responses of several independent input variables.[113] RSM, along with machine learning regressions (MLR); a method used to investigate the relationship between independent variables and a dependent variable or outcome. Both RSM and MLR can be valuable predictive tools, reducing the need for unnecessary experimentation when an optimal set of parameters with a high degree of confidence can be computed.[114]

RSM has been extensively studied with regard to obtaining consistent fiber diameters,[115] tunable fiber orientation,[116] pore size and fiber quality,[117] and determining the number of beads and bead size.[114] Interpolation machine learning models, such as Kriging,[118] artificial neural networks (ANNs),[119] and grey-correlation analysis (Grey theory),[120] are powerful tools in understanding unknown nonlinear processes. These methods have provided insightful studies focused on determining and analyzing fiber diameter.[121]

Theoretical modeling, along with experimentation, can be vital in better understanding the variant processes described in the following section, and by doing so, can significantly improve reproducibility and fiber output.

3.6. Classification

The electrospinning techniques introduced in this review are categorized based on spinneret configuration into two groups: needle-based and needleless. Six needle-based electrospinning techniques (mono-axial, co-axial, tri-axial, centrifugal, 3D, and handheld electrospinning) and five distinct needleless high-throughput technologies (roller, bubble, corona, wire, and high-speed electrospinning) were identified and are summarized in **Table 4** below.

4. Advanced Electrospinning Technologies: Needle-Based

4.1. Mono-Axial

Introduced by Cooley and Morton in 1902, mono-axial is the first and most commonly used electrospinning method that evolved

Table 4. Classification of electrospinning techniques.

Needle-based	Needleless
• Mono-axial	• Roller
• Co-axial	• Bubble
• Tri-axial	• Corona
• Centrifugal	• Wire
• Three-dimensional (3D)	• High-speed
• Handheld (in situ)	

from electrospraying.[26,27] As previously described, a conventional mono-axial setup consists of a high-voltage power supply, a syringe container with a single metallic hollow capillary (blunt metallic needle), and a counter electrode collector placed at a specific distance from the oppositely-charged needle, horizontally or vertically.[103]

A schematic diagram of the mono-axial electrospinning method can be seen in Figure 2a. First, a polymer solution of predetermined composition is loaded into a syringe and withdrawn at a controlled rate using a syringe pump, producing a liquid hemisphere droplet at the tip of a blunt metallic needle (the spinneret). The electrostatic charges build up at the surface of the liquid droplet due to the high voltage applied to the metallic needle. When the electric field exceeds a specific value, the electrostatic forces overcome the surface tension of the polymer solution or melt, instigating Taylor cone formation from the apex of the liquid droplet. Jetting occurs due to the electrohydrodynamic stresses present in the travel path (referred to as working distance), the linear region between the spinneret and the collector. As the jet expands toward the collector, it becomes thinner, resulting in the rapid evaporation of the solvent, leaving behind solid polymer fibers to be deposited on the collector.[53] Variations of the mono-axial electrospinning setup include linear or circular motion multi-spinneret systems consisting of multiple mono-axial needles.[122] This approach has been reported to be ineffective for the high-throughput production of NFs due to electrostatic interactions between nearby needles and needle clogging, although it is still employed by some high-throughput electrospinning systems today. The most important advantages and disadvantages of mono-axial electrospinning can be found in **Table 5**.

To some extent, the limitations associated with the fact that mono-axial electrospinning can only be used to produce fibers derived from a single solution can be circumvented via sequential electrospinning, co-electrospinning, or electrospinning-co-electrospraying. Sequential electrospinning refers to electrospinning solution A for a predetermined amount of time, then changing to solution B and continuing with the electrospinning process onto the same fiber deposition, and so on. Co-electrospinning/electrospraying, or concurrent electrospinning and electrospraying, uses a rotating mandrel as the collector, and two spinnerets fed to two distinct reservoirs are placed antiparallel or vertically and horizontally to one another to electrospin/spray simultaneously onto the same collector. This simple tweaking of mono-axial electrospinning process can enhance the complexity of the attained electrospun mats, producing structures such as layer-by-layer or mixed membranes that encompass properties derived from two or more polymer solutions in a layer-by-layer configuration.[123,124]

Table 5. Advantages and disadvantages of mono-axial electrospinning.

Advantages	Disadvantages
1. The spinneret consists of a single needle, making the setup less complex and easy to operate.	1. Limited production capacity. The yield of dry solid fibers via mono-axial electrospinning is 0.01–0.3 g h^{-1}, making it suitable only for laboratory use or projects requiring small fiber outputs, e.g., sensor electronics, where a thin layer of NFs can be used as interface materials.[125]
2. Irrefutably the most well-studied electrospinning method, it can assess the spinnability of new materials and complex composites or optimize the solution, process, and ambient parameters before production on a large scale.	2. The NFs present a simple structure, presenting a circular cross-section with a smooth surface. When applied to drug delivery platforms, the lack of a complex fiber structure encourages an initial burst release of the incorporated compound. Although solvent–drug and polymer–drug compatibilities can be employed to control the drug release rate, mono-axially produced NFs perform poorly in sustained release profiles.[4]
3. Reproducible fine fibers can be obtained in the lower range of the nanoscale. In addition, distinct micromorphologies (such as randomly oriented or aligned fibers) can be obtained by adjusting the solution, process, and ambient parameters, the needle's inner diameter (e.g., gauge), and the type of collector (e.g., flat, drum, or liquid bath).	3. The fabricated scaffolds present a 2D network of small-diameter pores and high pore interconnectivity. The fibrous membranes become too compact under prolonged spinning periods, often performed to attain mechanical stability. Although overcoming the small pore size constraints associated with this method can, in some instances, be achieved by postfabrication processing methodologies capable of widening the pores (such as cryogenic electrospinning[126] and gas-foaming[127]), in general, the pores produced via this technique are too small for the penetration of large particle and the majority of mammalian cells.[128]
4. Multineedle electrospinning apparatuses capable of facilitating high-throughput production are currently on the market.	4. Multineedle electrospinning apparatuses are challenging to operate and inconsistent due to electrostatic interactions between nearby needles and needle clogging.

4.2. Co-Axial Electrospinning

Co-axial electrospinning is a variation of the conventional electrospinning method invented by Sun et al. in 2003.[37] Co-axial electrospinning enables independent reservoirs of two different solutions fed onto a co-axial needle to form single composite fibers that present a core/shell morphology.[129] The co-axial spinneret consists of a double capillary compartment arranged concentrically, with the inner needle fitted within the outer needle. Independent solutions travel to the orifice of the co-axial needle from separate pumps, where the flow rates are adjusted accordingly. The inner capillary contains the core solution, while the outer capillary produces the shell polymer.[130] At the orifice, a compound Taylor cone forms as the shell polymer solution entraps the core fluid and is subjected to an applied electric field, conceptually similar to conventional electrospinning.[59] After the solvents evaporate, a heterogeneous but continuous fiber composed of the core and shell constituents is collected.[131] The basic concept of co-axial electrospinning is illustrated in **Figure 5**, and the limitations and advantages of the technology are summarized in **Table 6**.

The interactions that govern the properties of the resulting core/shell fibers are determined by the degree of rheological, physical, and chemical dissimilarities between the two solutions.[132] However, a uniformly assembled core/shell fiber can only form if a stable Taylor cone is maintained. Processing parameters related to co-axial electrospinning have been reviewed in the literature,[133,134] with the studies agreeing that the complexity of co-axial electrospinning originates from the difficulty in maintaining a stable Taylor cone. To induce a stable Taylor cone, process parameters should be such that 1) an electrospinnable shell solution is used; 2) the shell solution viscosity is higher than the core solution viscosity, so that the stress relating to the viscosity between the core and shell solutions overcomes the interfacial tension between them;[135] 3) a low vapor pressure solvent is used (as fast evaporation may destabilize the Taylor cone); and 4) the conductivity of the shell solution is greater than that of the core solution to inhibit core/shell structural discontinuities induced by the rapid elongation of the core polymer.[132]

Co-axial electrospinning is an advantageous method since it can produce fibers with novel structures out of highly diverse polymer pairs (Figure 5d); core–sheath, hollow, and nanoparticle-decorated, with each component maintaining its separate material identity.[133] By exploiting this feature, sophisticated pairs of materials can unify their properties into a single composite fiber. Highly unstable materials, such as enzymes, growth factors, and rapidly degradable compounds that would otherwise be rapidly broken down within an intricate niche, can be preserved by the sheath material.[136] For this reason, the properties of polymers can be manipulated while employing the co-axial electrospinning technique, which is of interest in the biomedical sector because it can be used to develop biocompatible and mechanically stable materials.[75] Co-axially electrospun fibers are widely employed to develop drug delivery systems that can attain a tailored substance release. Through this process, nanofibrous scaffolds with superior properties to those of monolithic fibers, including a hydrophilic surface within a hydrophobic core, adjustable mechanical properties, and the controlled release of defined concentrations of active pharmaceutical compounds or nanomaterials, can be fabricated.[132]

4.3. Tri-Axial and Multi-Axial Electrospinning

As the name indicates, the tri-axial electrospinning process uses a tri-axial spinneret made of three concentric needles capable of simultaneously infusing up to three different materials. As with co-axial, tri-axial electrospinning belongs to the multi-axial electrospinning family, with variations reported that include quadraxial and multi-nozzle. **Figure 6**a shows a typical layout of a tri-axial electrospinning setup, which consists of four modules: three individual solution pumps, a high-voltage power supply, a grounded or negatively charged collector, and a spinneret comprised of three concentric needles. Three pumps are used at adjustable feeding rates to drive up to three individual working solutions, referred to as outer, middle, and inner. As with all the multi-axial technologies, this method can be also employed to electrospin materials that are not solely electrospinnable. The simultaneous feeding of the three solutions forms a composite Taylor cone when an appropriate voltage is applied to the system. Ultimately, trilayer-structured composite fibers can be deposited on the collector.[131] Foreseeably, all the process parameters that need to work synergetically to obtain a stable Taylor cone in co-axial electrospinning are applicable in tri-axial electrospinning but at an even greater complexity. For this reason, since multi-axial fibers were first reported in 2009 by Kalra and co-authors,[40] only a small fraction of electrospinning research has been focused on multi-axial setups, with only 46 articles published since that date (based on a Scopus search for “triaxial electrospinning” OR “tri-axial electrospinning” OR “multi-axial electrospinning” OR “multi-axial electrospinning AND LIMIT-TO (DOCTYPE , "ar")”).

Figure 6b indicates an SEM image of the trilayer structure. The trilayer structure adds extra complexity to the properties of the composite fibers due to the possibility of introducing different functionalities and compositions through the different layers, finding applications in a broad range of fields and, most significantly, in drug delivery.[147] The trilayer structure can function as a single carrier of multiple substances, adding an extra layer of protection from polymer degradation due to external stimuli.[121] As shown in Figure 6b,c, taking advantage of this concept, composite polymer NFs containing different drugs or variant drug concentrations can be incorporated within the three-layer format. In this regard, the drug concentration will indicate a gradient distribution from the inner core, containing the highest concentration, to the outer shell, containing the lowest concentration. Furthermore, due to the inherent advantages of the trilayer structure, under the premise of Fick’s law of free diffusion, the drug release rate from the inner core layer will be further retarded, as it must first diffuse through the intermediate layer before reaching the sheath, gradually increasing in concentration from the inner to the outer layer, and thus resulting in extended release, programmable based on the chemistry of the sheath and the diffusability properties of the intermediate layer.[148] **Table 7** summarizes the advantages and disadvantages of the process.

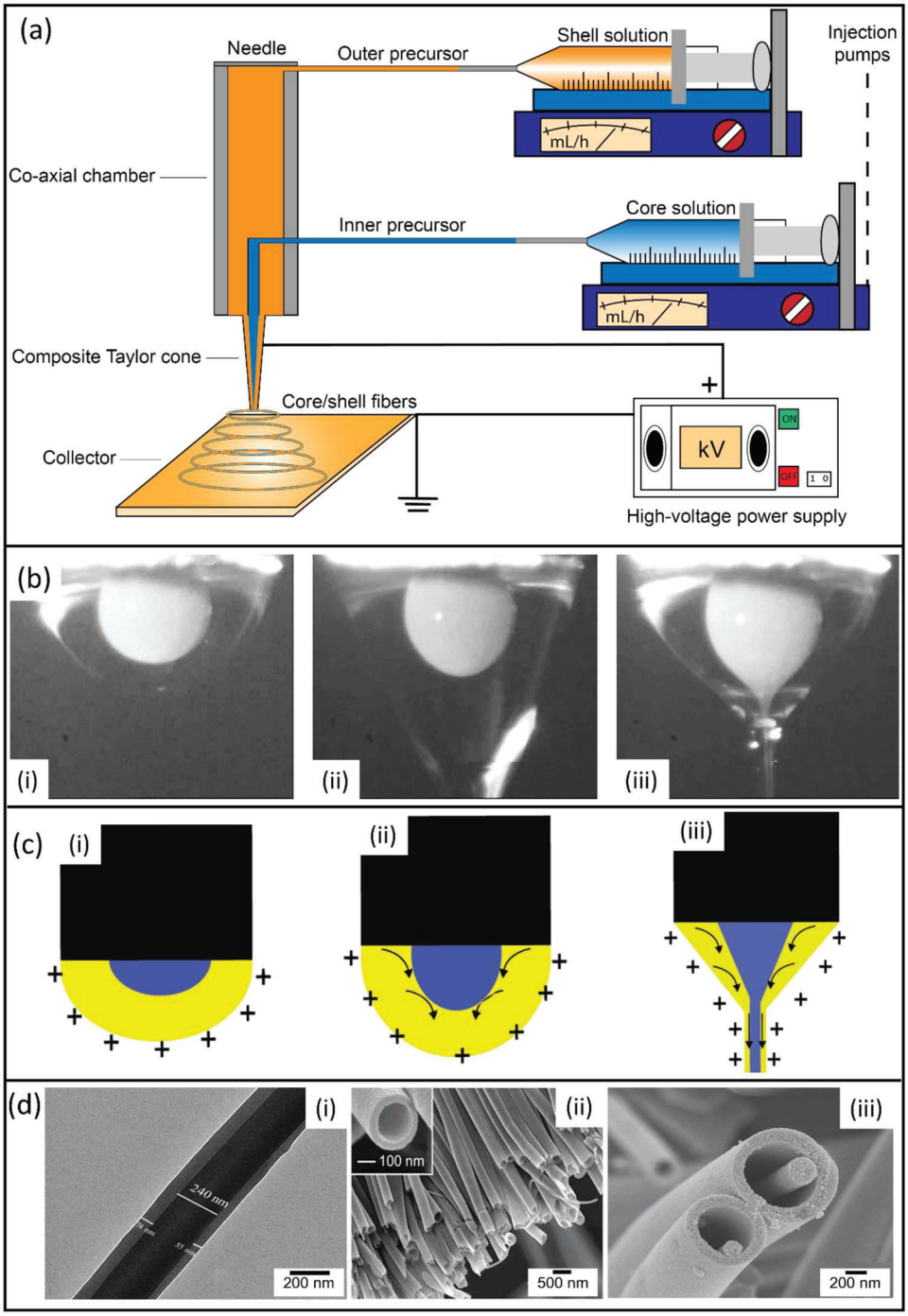

Figure 5. Generation of co-axial electrospun fibers. a) Schematic of a standard co-axial electrospinning setup; b) configuration of the co-axial Taylor cone, following the evolvement of the electrified jet as the voltage amply increases, where polyvinylpyrrolidone (PVP) is the shell and mineral oil is the core solution;[137] c) schematic representation of the charges forming the co-axial Taylor cone, i) surface charges develop around the surface of the shell solution, ii) a viscous electrified strain exerts the droplet causing it to be deformed, iii) a stable core–sheath jet develops. d) SEM images of i) core/shell,[138] ii) hollow,[68] and iii) nanowire-in-microtube structured fibers.[139] Copyrights: (b) Reproduced with permission.[137] Copyright 2017, Elsevier; (d) (i) Reproduced with permission.[138] Copyright 2019, American Chemical Society; (d) (ii) Reproduced with permission.[68] Copyright 2004, American Chemical Society; (d) (iii) Reproduced with permission.[139] Copyright 2010, American Chemical Society.

Table 6. Advantages and disadvantages of co-axial electrospinning.

Advantages	Disadvantages
1. Co-axial electrospinning can form novel core–shell fiber structures where the activity of the core compound can be protected by the external environment through the sheath material. Core/shell fibers have applications in nanocatalysis,[140] fiber-reinforced composites,[141] smart textiles,[142] energy storage,[143] and filtration[110] but predominately for biomedical applications, such as tissue engineering, drug delivery, and antimicrobial surfaces.[4,75]	1. The process is complex. Co-axial electrospinning requires a specialized spinneret consisting of two concentrically aligned needles that dispense two distinct solutions through two individual syringe pumps. This increases the complexity of appropriately adjusting the process parameters. Additionally, co-axial needles are expensive to purchase, while cleaning procedures for clogged needles can be time-consuming and arduous, as needles are not as often discarded, especially during the early stages of evaluating the compatibility of the core and shell solutions.
2. Hollow NFs can be formed by selectively removing the core material (e.g., chemically or thermally) from the core/shell structure post-fabrication.[140,144]	2. The process is difficult to implement. The core and shell solutions co-electrospun through a single orifice require good compatibility and similar physicochemical properties to prevent separation and attain a homogenous core/shell cross-section.
3. Core/shell drug-loaded fibers can retard the release kinetics of a substance, preventing the initial burst release commonly associated with monolithic fibers. This way, different controlled-release drug delivery systems requiring substantially smaller concentrations of a given substance can be attained. Although the core/shell chemistry and surface properties can be modified depending on the desired release mode, in general, the drug loaded into the core compartment of the structure is released by permeation through the outer shell of the polymer fiber and degradation of the shell.[145]	3. A balance between the flow rate of the two solutions is required to obtain a homogenous distribution of the shell component within the core–shell structure. However, achieving this balance can be difficult as it requires tuning of the interfacial tension, viscosity, solvent volatility, and conductivity between the two independent solutions to ensure comparable flow rates. Differences in the extrusion rate will result in inhomogeneous compound fibers. For example, a low shell flow rate may disrupt fiber formation, whereas a higher flow rate produce a fragmented sheath structure.[146]
4. This process makes it feasible to electrospin materials that are not electrospinnable per se due to their chemistry (such as oligomers) by accommodating them within the fiber's core if the core and shell solutions are sufficiently compatible.	

4.4. Centrifugal Electrospinning

Centrifugal, or rotary jet, electrospinning (CES) is a modified technique that combines electrospinning and centrifugal spinning principles (**Figure 7** and **Table 8**). In traditional centrifugal spinning, spinning is initiated by the centrifugal force acting on the jet, which is influenced by the mass of the polymeric solution, the angular velocity, and the radius of the centrifugal disc (the distance between the spinneret and the collector).[153]

The first CES apparatus was created by Andrady et al.[38] in 2005. A CES apparatus consists of a rotary feeding plate (spinneret), a high-voltage power supply, a feeding channel, a motor, and a collector. The key feature of this technology is the use of a high-speed motor to rotate the spinneret and, in some instances, the collector. Following the same electrospinning principles, high voltage is applied between the rotary feeding plate and the collector. The spinneret consists of needles evenly distributed around the edges of a disk, although needleless rotating spinnerets have also been reported in the literature.[154] The collector can be a cylindrical stationary plate where fibers are deposited horizontally in a downward or upward motion, or a ring/multiple-pole circularly-arranged metal strips/wires collector surrounding the spinneret, where fibers are collected either in a static or motion mode. As the polymer is fed into the spinneret, the spinneret's rotation speed must be appropriately adjusted to allow for Taylor cones to form at the end of each needle as the solution is evenly extruded and electrified. The synergetic effect of centrifugal and electrostatic forces governs the formation of Taylor cone, resulting in higher production rates of fiber than the conventional electrospinning method while requiring a lower working voltage or rotating velocity than the individual techniques. When the combined forces overcome the polymer droplet's surface tension and viscous resistance, jetting initiates and ultrafine NFs form. The facile mechanical rotation and lower voltage requirements make CES the best-reported technique for achieving highly aligned NFs.

Recently, Norzain and Li[153] proposed a mathematical model based on Newton's second law taking into account the several forces the polymeric jet is subjected to during CES; centrifugal force, electrostatic force, surface tension force, and viscous force. As reported in two publications, Erickson et al. have developed highly uniform (based on the fiber diameter standard deviation), uniaxially aligned, chitosan (CS)-PCL and hyaluronic acid-coated NFs, illustrating the importance of fiber orientation in influencing tumor cell motility and tissue topography.[155,156] Works by Wang et al.[157,158] explored the effects of dual-rotation CES, where both the spinneret and collector rotate in the same, counter, or multidirectional orientation while assessing a range of polymers: PVP, polystyrene, PCL, and thermoplastic polyurethane (TPU) toward the development of complex drug release matrices, based on the fiber's morphological properties. Yanilmaz and Zhang[159] used this technique to develop polyacrylonitrile/polymethylmethacrylate (PAN/PMMA) carbonized NFs as a separator material for Li-ion batteries. The authors reported that compared to microporous polyolefin membranes, the centrifugally electrospun PMMA/PAN membranes presented better ionic conductivity, higher electrochemical oxidation limit, and lower interfacial resistance coupled with lithium.

Among the notable attempts to improve the process parameters, Valipouri et al.[160] developed an air-sealed setup that improved the stability of the jet, a commonly reported issue of CES. Kancheva et al.[161] achieved radial fiber deposition of highly

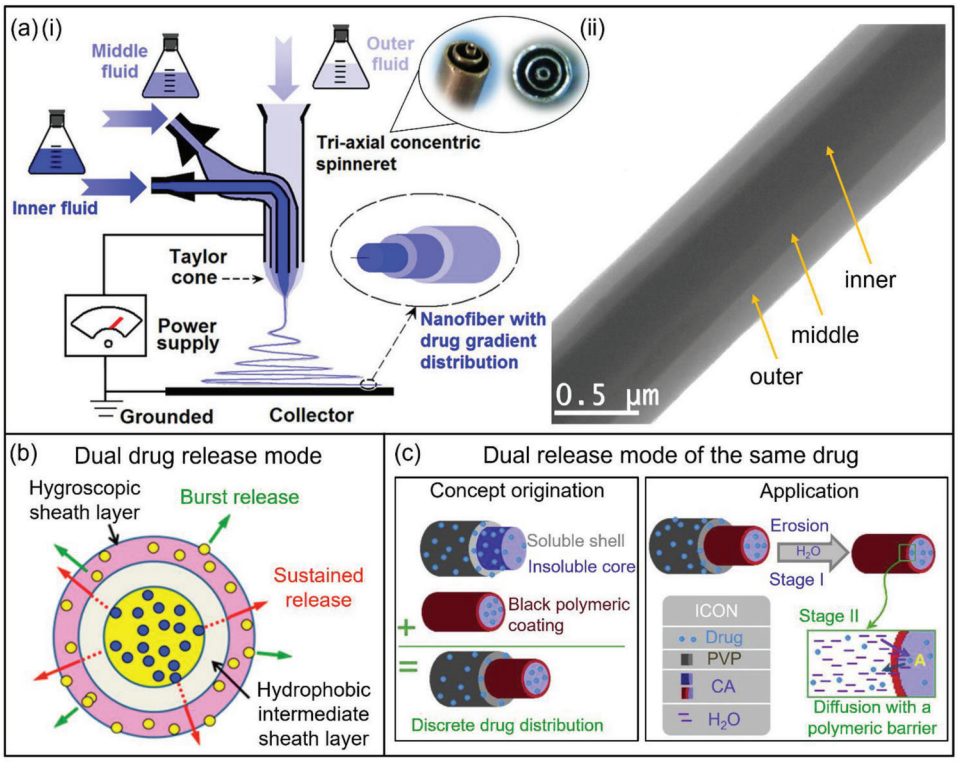

Figure 6. The tri-axial electrospinning process. a) Tri-axial spinneret: i) Illustrative diagram of the setup; ii) SEM image of a trilayer structure. Adapted from ref. [147]. b) Transmission electron microscopy (TEM) cross-section depiction of tri-axial fiber loaded with two different substances, consisting of a PVP core loaded with Keyacid Blue (blue particles), a PCL intermediate layer, and a PCL outer layer loaded with Keyacid Uranine (yellow particles). Adapted from ref. [149]. c) Schematic depiction of a dual drug release system of the same substance. This system consists of a burst release (42% of the loaded drug within 2 h) of ketoprofen through a water-soluble outer sheath (PVP) and the subsequent sustained release (90% of the loaded drug within 60 h) of ketoprofen-loaded CA core by retarding its release through an intermediate layer of blank CA. Adapted from ref. [150]. Abbreviations: PVP, polyvinylpyrrolidone; PCL, polycaprolactone; CA, cellulose. Copyrights: (a) Adapted with permission.[147] Copyright 2015, American Chemical Society; (b) Adapted with permission.[149] Copyright 2013, American Chemical Society; (c) Adapted with permission.[150] Copyright 2020, Elsevier.

Table 7. Advantages and disadvantages of tri-axial electrospinning.

Advantages	Disadvantages
1. Tri-axial electrospinning has distinct advantages over other electrospinning methods due to its ability to form complex multilayer nanostructures. By alternating the physicochemical properties of each layer, this methodology finds applications in tissue engineering, where mechanically durable synthetic materials can be integrated within the core structures, allowing naturally derived materials, which may lack mechanical stability, to be included in the outer layer, enhancing, for instance, cell adherence and proliferation.[147,151]	1. The design of the concentric spinneret plays an essential role in the success of the process: variations in the intraneedle spacing and inner diameter between the concentrically aligned needles can positively or negatively affect the distribution of each material within the compound fiber during Taylor cone formation and jetting.[152]
2. Tri-axial electrospinning can overcome problems associated with limited drug solubility. This method can be used to load sensitive substances such as small molecules, proteins, and growth factors that may present inadequate drug release kinetics and be sensitive to pH fluctuations and the presence of harsh media. In such instances, tri-axial fibers could allow for the release of the desired compound to the appropriate tissue site (e.g., a tumor).[148]	2. The quality of the spinneret. A good tri-axial spinneret must be durable to obtain reproducible results by withstanding harsh washes and erosion from solvents.[53] Furthermore, the electrical distribution through the outer needle material must be sufficient and stable enough to electrify the composite fluid at the point of eruption.
3. Tri-axial electrospinning can create tunable drug release kinetics and transport mechanisms, such as multistep diffusion drug delivery systems. Tri-axial fibers can incorporate multiple single-substance drug release profiles or the possibility of loading variant substances in each compartment.[149,150] This way, for instance, combining an initial burst release (e.g., immediate-release and first-order systems) with a controlled-release profile (e.g., zero-order release) is feasible.	3. General difficulties of implementation. It can be challenging and, in many instances, improbable to attain three compatible spinning solutions with similar physicochemical properties to prevent separation. Even if that is feasible, it is exceedingly difficult to synchronize the inner, intermediate, and outer flow rates to form a well-distributed compound Taylor cone and keep the concentric structure continuous through the entire process, primarily due to gravity and surface tension effects.

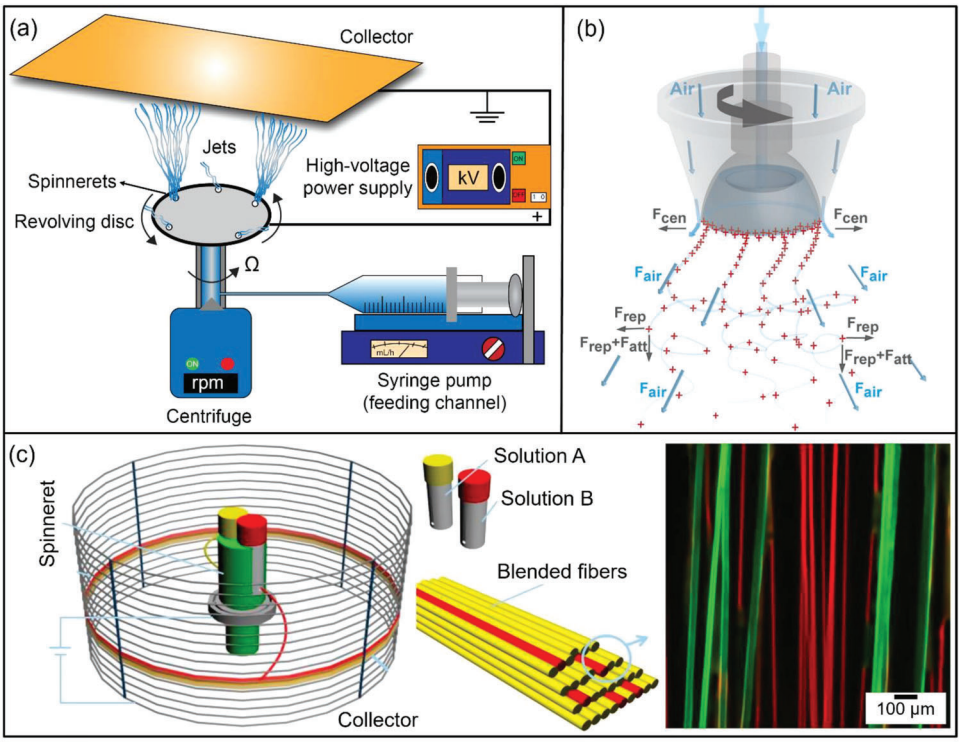

Figure 7. Centrifugal electrospinning. a) Schematic of the CES process. b) Diagram depicting the electric repulsion and centrifugal forces that work synergetically to overcome the solution's surface tension at the spinneret's surface and induce fiber formation. A rotating disk, attached to a motor comprised of multiple pits (spinneret exits), discharges polymeric solution at a controlled rate via a syringe pump system. An applied voltage and the rotational velocity of the disk facilitate the formation of multiple Taylor cones, which, via high frequency of rotation, expand to form ultrathin fibers. Reproduced from ref. [164]. c) Development of aligned multicompartment composite microfibers at 120 g h^{-1} production rate. On the left is a schematic of the CES setup consisting of a double solution reservoir at the spinneret and an iron wire ring collector. On the right is a fluorescence image indicating the successful production of blended aligned fiber configurations. Abbreviations: Ω, angular velocity; F_{cen}, centrifugal force; F_{rep}, electrostatic repulsion; F_{att}, attraction toward the collector; F_{air}, guiding air. Reproduced from ref. [158]. Copyrights: (b) Reproduced with permission.[164] Copyright 2020, American Chemical Society; (c) Adapted with permission.[158] Copyright 2018, Springer Nature.

Table 8. Advantages and disadvantages of centrifugal electrospinning.

Advantages	Disadvantages
1. Ultrafine alignment in the micro- and nanoscale can be attained much more straightforwardly than through conventional electrospinning due to the combined effect of electrostatic and centrifugal forces. Furthermore, in general, the process requires lower jet initiation voltage and rotating speed, which can improve the operational safety of the process by reducing injuries associated with high-voltage and high-speed centrifugation.[160]	1. CES is a relatively new method, with approximately a hundred articles published. Due to the integration of a centrifuge compartment, the design and development of CES (especially toward the spinneret and collector configuration) are more complex. As such, during CES additional process parameters must be investigated and optimized for successful fiber production.[141]
2. CES primarily produces loosely packed microfibrous structures that display fiber directionality with larger mean pore sizes.[165] This can find applications in tissue engineering and scaffold development.	2. One of this method's limitations is the difficulty of incorporating active substances due to the absence of a complex hierarchy.[166] Early reports of co-axial CES fibers have recently been published,[163] but further research is required.
3. CES can be used to electrospin higher concentration solutions, and polymer melts through the additional centrifugal forces applied into the system, assisting fluid transport where jet initiation may not be feasible due to increased viscosity.	3. The majority of CES reserach has concentrated on spinneret configuration using mon-axial needle or needle-like arrays designs. Although due to the centrifugal forces and the ability to distribute the individual nozzles in a 360° format, near-electric field effects are not considered an issue, nozzle clogging and off-target fiber jetting can still occur (especially toward nearby needles), making the process laborious to set up and clean.
4. Capable for scale-up. A higher fiber production rate is feasible due to the synergetic effect of the two processes, allowing jetting to occur at increased extrusion rates and through the ability to collect fibers in a 360° collector configuration.[141] In addition, needleless CES is feasible, although further research is needed.	

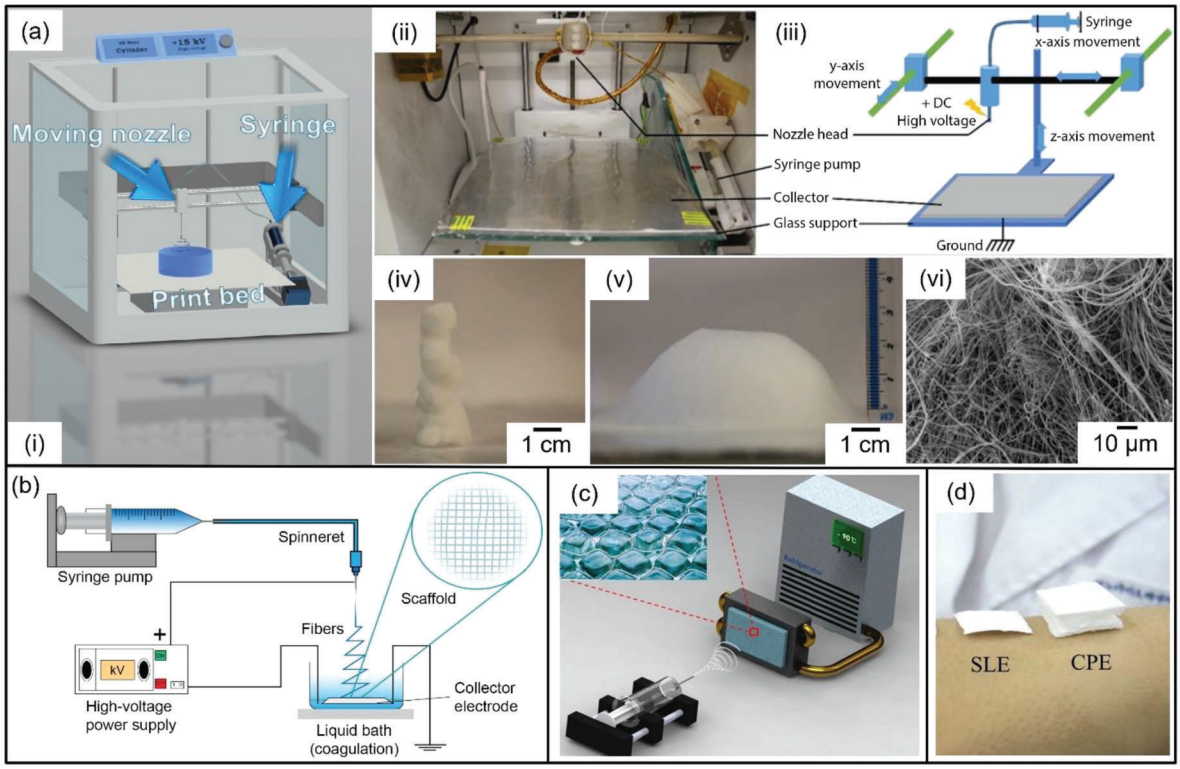

Figure 8. 3D electrospinning technologies. a) 3D electrospinning setup combining conventional electrospinning and 3D printing, i) schematic illustration of the setup; ii) photograph of the 3D electrospinning device; iii) schematic representation of the device aspects of the apparatus; iv–v) obtainable 3D structures; vi) SEM image of the 3D deposited fibers. Adapted from refs. [169,170]. Schematic of the b) wet electrospinning and c) cold-plate electrospinning technique. Adapted from ref. [171]. d) Photograph comparing 3D fibrous scaffolds produced by salt-leaching electrospinning (SLE) and cold-plate electrospinning (CPE). Modified from ref. [50]. Copyrights: (a) (i) Reproduced with permission.[169,170] Copyright 2020, Elsevier; (a) (ii–vi) Adapted with permission.[169,170] Copyright 2021, Elsevier; (c) Reproduced with permission.[171] Copyright 2016, Elsevier; (d) Adapted with permission.[50] Copyright 2015, Elsevier.

aligned fibers (fiber diameter 550 ± 90 nm) and produced electrospun mats with a large area (2200 cm^2) within 20 min. In this work, fiber alignment was achieved when using circularly-arranged metal strips as the collector but not with a cylindrical collector (at a rotating speed of 1900 rpm). Chang and co-workers studied the effects of a viscoelastic jet during CES and mathematically described, through dimensionless number and group analysis, that the strong stretching force and a fast extension speed obtainable during the process can significantly reduce the effect of the whipping instabilities and fabricate a series of uniaxially aligned polymeric NFs with improved physical properties such as high modulus, hardness, crystallinity, and good molecular orientation.[162] For the first time, Gu et al.[163] recently addressed the development of complex NF structures via the CES technique by integrating CES with co-axial electrospinning to produce core–sheath structures out of poly(vinyl alcohol) (PVA) (core) loaded with paclitaxel and poly(L-lactic acid) (PLLA) (shell), with a controllable drug release profile by adjusting the thickness of the sheath material.

4.5. 3D Electrospinning

A significant restraint of conventionally produced electrospun membranes is their inherent 2D structure. This hinders the ability to develop a highly porous 3D structure, which can benefit fields such as complex 3D tissue models with improved cell infiltration, and wound healing[143] (**Figure 8** and **Table 9**).

Initially, significant research focused on postprocessing, multilayering, and template-assisted electrospinning techniques to obtain 3D built-ups.[66] Postprocessing techniques involve producing 2D electrospun membranes and folding, freeze-drying, and gas-foaming the structure to create a 3D version from 2D electrospun mats. As the name suggests, multilayer electrospinning involves compiling multiple layers of sequential electrospun or co-electrospun materials. Finally, the template-assisted method consists of electrospinning onto a sacrificial 3D template, such as mechanical and matrix templates, which subsequently leached (postprocessing), leaving behind a 3D fibrous structure. Nonetheless, although these approaches have seen significant recognition in the literature, they cannot be considered 3D electrospinning technologies, as they cannot directly produce 3D electrospun structures.

Two variations of conventional electrospinning, i.e., wet and cold-plate electrospinning, and one self-assembly-inspired electrospinning apparatus that integrates 3D printing and electrospinning principles to produce CAD-assisted 3D micro/nanofibrous configurations, are the only technologies, to date, capable of instantaneous one-step production of 3D electrospun structures (Figure 8a).

Table 9. Advantages and disadvantages of 3D electrospinning.

Advantages	Disadvantages
1. It is one of the most straightforward and advanced techniques to manufacture 3D structures with tunable morphology, pattern, and physical and chemical properties.	1. Nano-microfiber blocks made by 3D electrospinning are soft and fluffy (woven); they have cotton-like structures when they are dry but often break down upon contact with a liquid, posing an issue for anisotropic lamellar deposition.
2. Due to non-contact operation and CAD-directed spinneret motion, 3D electrospinning is the only reported technology capable of directing the morphology of the 3D structures without requiring subsequent post-fabrications steps.	2. Polymer systems with higher conductivity are necessary for 3D assembly, hence narrowing the class of materials that can be used.
3. Waste produced is reduced via 3D electrospinning, as it does not require post-fabrication procedures to obtain 3D scaffolds.	3. Increasing the height of the constructs decreases the precision of the process, limiting upscaling.
4. CPE can produce nonwoven, microporous structures with better mechanical stability than 3D electrospun structures.	4. 3D electrospinning methodologies such as CPE, are limited to water-soluble polymers, require significant post-fabrication processing and can only attain random 3D macro-architectures. Similarly, wet electrospinning is limited by the range of coagulation solvents available for a specific polymer. Furthermore, the depth of the bath (from the bottom where the electrode is placed to the bath's surface) limits the upscaling of the process and the ability to produce diverse 3D structured macromorphologies.

Yokoyama and co-authors first described the wet electrospinning technology in 2009 as a novel method capable of fabricating 3D spongiform NFs.[44] The process is conceptually similar to conventional electrospinning, with the key difference being the use of a bath as the collector filled with a low surface tension solvent (e.g., tertiary-butyl alcohol), which is capable of solidifying and attracting the formed fibers [e.g., poly(glycolic acid)], toward a grounded metallic plate placed at the bottom of the bath (Figure 8b). This process produces nonwoven 3D structures that are relatively short, with a low bulk density and high porosity. Following the same principles, Ghorbani et al.[167] produced PLA porous 3D scaffolds in a sodium hydroxide (NaOH) bath for wound healing applications. Zhang et al.[150] employed this technology to produce *Rana chensinensis* skin collagen (RCSC)/poly(ε-caprolactone) (PCL) Ag nanoparticle-loaded in an ethanol bath, creating 3D porous nanofibrous materials with ≈90% porosity.

Sheikh et al.[50] described the cold-plate electrospinning technique in 2015 when they produced 3D silk fibroin large-pore nanofibrous scaffolds (Figure 8c,d). During cold-plate electrospinning, as the name suggests, a collector plate is placed over a heat transfer pipe connected to an immersion chiller that can lower the plate temperature to −90 °C, at which ice crystals form, enhancing the conductivity and subsequently instigating the deposition of the fibers in a layer-by-layer format. In this work, silk fibroin was blended with PEO, where the scaffolds produced were subsequently freeze-dried, immersed in ethanol for crystallization, and finally immersed in deionized water to remove the carrier polymer (PEO). The 3D scaffolds improved cell infiltration in vitro (using human dermal fibroblasts and keratinocytes), compared to the NFs obtained using conventional electrospinning due to the higher porosity and larger pore sizes attained via this methodology.

Although the above technologies can produce 3D structures through electrospinning and have gradually evolved since they were first introduced in 2005,[143] after subsequent exploration,[168] 3D fibrous self-assembly via electrospinning, an exciting single-step fabrication method of producing 3D electrospun structures, was developed. 3D electrospinning is the first technology that combines electrospinning and extrusion-based 3D printing to develop CAD-assisted 3D fibrous patterns.[51] Vong et al.[51] first described this technology in 2018, demonstrating the controlled deposition of 3D buildup by including a conductive additive in the electrospinning solution (H_3PO_4). It is a non-contact printing technique suitable for fabricating complex and nonplanar surfaces. Complex electrospun 3D structures benefit from various biological, mechanical, and mass transport properties. A 3D electrospinning setup possesses a high-voltage source and solution controller with a fused deposition modeling 3D printer, which provides the *x*-*y*-*z* motion control. The polymeric solution is fed into the moving nozzle, connected to a high voltage that allows the directed deposition of 3D structures. The guided NF assembly process forms these structures into shapes due to electrostatic induction, rapid evaporation, and polarization.[146] In follow-up work, Vong et al.[169] analyzed the mechanism behind the 3D buildup, demonstrated that the incorporation of electrodes can further enhance the shape of the produced structures at the collector's surface, and demonstrated the upscaling of the process, creating 3D macrostructures up to 5 cm in height out of polystyrene, polyacrylonitrile and polyvinylpyrrolidone within 10 min.

4.6. Portable Electrospinning

Portable electrospinning refers to handheld and lightweight electrospinning devices designed to produce fibers on-site (**Figure 9** and **Table 10**). The technology was inspired by wound care and management as an alternative approach to simultaneously achieving hemostasis, wound protection from infection, and promoting tissue regeneration.[172] The inspiration behind the development of in situ fiber deposition onto a wound was transduced by this approach being able to provide painless personalized deposition of lightweight dressings directly on the injured site.[66] The initial drawback of the portable electrospinning de-

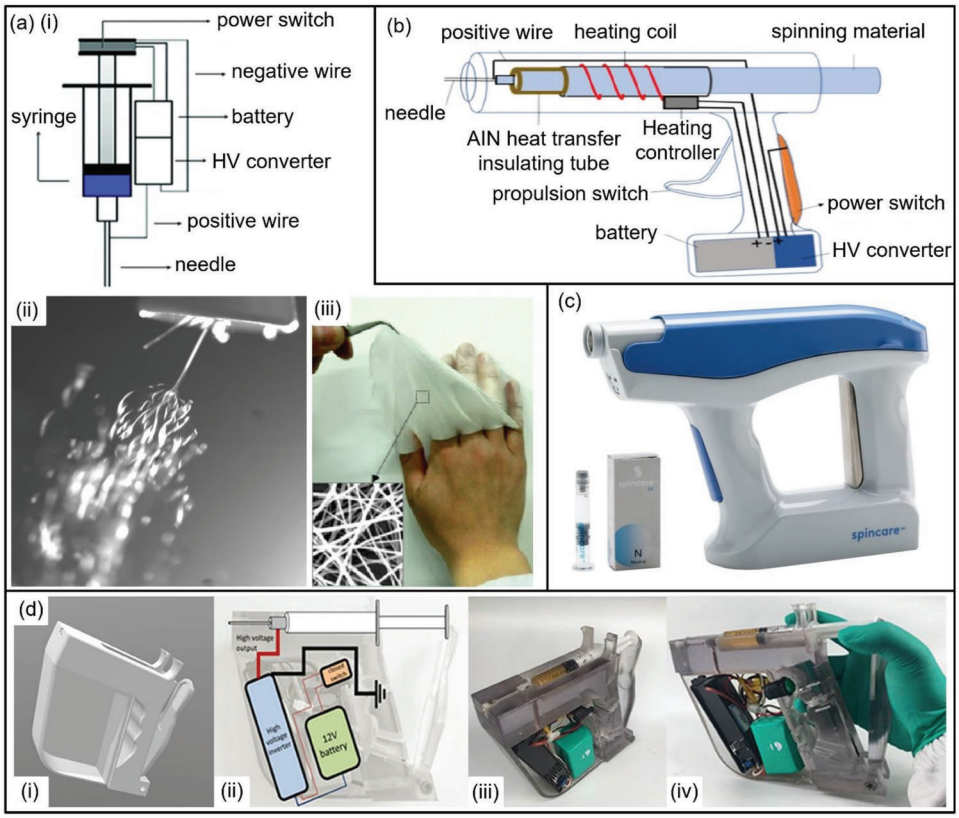

Figure 9. Portable electrospinning apparatuses. a) A representative depiction of a portable electrospinning device. i) Schematic diagram of its compartments; photographs of ii) jetting and iii) in situ fiber deposition onto a hand. Adapted from ref. [174]. b) A schematic diagram of a portable melt-extrusion electrospinning device. Adapted from ref. [183]. c) A photograph of the commercially available portable electrospinning device, currently undergoing clinical trial for its application in wound management (Spincare, Nanomedic, Israel). d) A 3D-printed apparatus. i) A rendered image of the CAD design; ii) a schematic of the electrospinning assembly, consisting of the 3D-printed compartments, a 12 V battery, a high-voltage converter, conductive wires for HV output, a syringe, and a metallic needle. iii,iv) Photographs of the assembled device. Adapted from ref. [182]. Copyrights: (a) Adapted with permission.[174] Copyright 2015, Royal Society of Chemistry; (b) Adapted with permission.[183] Copyright 2020, Springer Nature; (c) Reproduced from Nanomedic Technologies Ltd.; (d) Reproduced with permission.[182] Copyright 2020, Frontiers.

vice first designed by Sofokleous et al. in 2013 was the requirement of a cord to power the high-voltage power supply, thus minimizing its accessibility and the notion of onsite use.[173] Xu et al. were the first to resolve this issue by miniaturizing an electrospinning apparatus by integrating a battery power source, producing a device with dimensions of $10.5 \times 5 \times 3$ cm^3, only weighing ≈120 g, naming it battery-operated e-spinning apparatus (BOEA). The compact structure produced fibers in a cordless, single-hand motion.[174] They were able to electrospun N-octyl-2-cyanoacrylate (hemostatic glue) with a range of polymers; PCL, PS, PVP, PLA, and PVDF. Subsequent apparatuses inspired by these findings further miniaturized the electrospinning equipment and focused on evaluating in situ wound healing repair in animal models.[175–177]

Several antibacterial polymer formulations have been successfully electrospun using handheld apparatuses to produce wound dressings, including PCL loaded with silver nanoparticles mesoporous silica nanoparticles (AgNP) and asymmetrically spun PVP iodine-loaded NFs (HHE-1; handheld portable electrospinning apparatus, Qingdao Junada Technology Co., Ltd.).[177] Recently, the same device has been used to deliver active herb extracts (Lianhua Qingwen Keli) incorporated within PVP blends.[178] Dong and co-workers used a handheld electrospinning device to electrospin a PCL blend incorporating aggregation-induced emission luminogens, a newly emerged group of photosensitizers able to generate reactive oxygen species, for the treatment of multidrug-resistant bacterial infection.[179] Earlier this year, Xu et al.[180] described for the first time the in situ electrospinning of PVA NFs incorporating bone marrow-derived stem cells (BMSCs) using a handheld apparatus for the treatment of non-healing wounds. Zhang et al.[181] developed a simple portable electrospinning device consisting of a syringe, a metallic needle, and a AA battery-powered high-voltage converter (where a 3 V battery can produce a 10 kV output) to in situ electrospin core/shell nanoparticles (NaYF4:Yb/Er@NaYF4:Nd@hypericin, 50 nm in diameter) blended with PVP dissolved in acetone (≈500 nm in diameter), to be used for photodynamic therapy; a type of treatment that can generate reactive oxygen species (ROS) to effectively eliminate bacteria under light irradiation.

Portable electrospinning has encouraged the establishment of an Israeli-based company, Nanomedic, which has successfully commercialized a handheld electrospinning device, SpinCare. The equipment is currently undergoing clinical trial for the

Table 10. Advantages and disadvantages of portable electrospinning.

Advantages	Disadvantages
1. Handheld battery-powered electrospinning devices are the only reported apparatuses capable of producing electrospun fibers on the spot. This gives the device distinct advantages in medical applications, especially in wound management, where fibers incorporating pharmaceutical compounds, growth factors, or even cells can be directly deposited in a layer-by-layer format in an open wound. In this way, patients have reported alleviated pain, while the most recent in vivo studies and ongoing clinical trials show promising results.[66]	1. This is quite a new technology, with only a handful of patents filled and 25 research articles published to date. The equipment design is complex, particularly in regards to ensuring patient compliance and safety with regulations.
2. By formulating and depositing the fibers on-site, the technology can be considered more economically friendly by limiting excess fiber deposition. It is also beneficial for unstable substances that may not survive prolonged storage periods, post-fabrication treatments, or sterilization protocols.	2. In general, the production of in situ electrospun fibers is challenged by poor stability during the fabrication due to the inability to retain consistent spinning, applying opposite potential charge (always grounded, with no collector), and working voltages that do not exceed 10 kV. These issues often result in inconsistent fiber morphologies of a single material of low histocompatibility. Improvements concerning the reproducibility, quality, purity, potency, and solvent toxicity of the fibers produced are required.
3. As a portable technology capable of rapidly producing lightweight dressings, it can be utilized by emergency medical services, fire and rescue services, and the military.	3. Currently, only a limited number of materials, mostly water-soluble, have been electrospun through this process, due to the limited selection of solvents and additives . It is necessary to produce a wider range of naturally derived and synthetic polymers through this process to gain better undertsanding of the process parameters. Further improving the devices' interface will be required to eliminate issues with residual solvents.

external treatment of burns and wounds, and as of this year, 44 participants have enrolled. Five case studies have been made available, including the treatment of a graft donor site area and partial thickness burns (clinical trial: NCT02997592).

Recently, Chen and co-authors[182] fabricated a 3D-printed handheld apparatus consisting of three compartments; a cover, a handle, and the main body using Objet350 Connex 3D. The authors made the standard template library (STL) files publicly available. Upon assembly, the handheld electrospinning device was powered by a 12 V rechargeable Li battery (acting as a voltage generator), capable of producing up to 10 kV DC high voltage. A high-voltage inverter was connected to metal shrapnel through a lead wire and was used to electrify the stainless-steel spinneret needle. The polymer solution was extruded through a syringe using a "gun motion" (finger extrusion) and was attained via a pistol palm extrusion introduced to high-voltage static. The authors used this equipment to successfully electrospin a PLA/gelatin blend, where they assessed the in situ repair of skin defects in vivo.

5. Advanced Electrospinning Technologies: Needleless

Considering that the production output of needle-based electrospinning devices is commonly meager, ranging from 0.01 to 0.3 g h^{-1},[184] scaling up the process has been progressively studied as a suitable approach for industrializing this fabrication process. One of the strategies that have progressed to overcome the limitations of this process is the development of nozzle-less electrospinning setups. This can be achieved by scaling up the spinneret's structure while retaining an energetically stable and well-distributed configuration.[185] Unlike multineedle electrospinning, in which the electric field around a given needle is affected by the nearby jets, which can produce inhomogeneous fibers, free-surface electrospinning is an alternative method of high-throughput production of fibers with no constraints of clogged needles, providing freedom over the spinneret's configuration.

In 2004, Yarin and Zussman initially described the production of free-surface NFs by placing a layer of polymer solution underneath a magnetic liquid that was overlapping a permanent magnet against a vertically placed oppositely charged magnet by applying high DC voltage.[19] A year later, Jirsak and co-workers patented a process in which a rotating charged electrode, immersed within a polymer solution, placed underneath a counter electrode, could fabricate NFs at an increased production rate, in an upward bottom-up motion, with the assistance of an airstream to increase the auxiliary drying efficiency of the system.[24]

Lukas et al.[186] developed an electrohydrodynamic theory that describes the self-organization of electrified liquid jets from an open flat surface, based on the fact that fibers can arise during electrospinning from linear clefts even without the support of a magnetic fluid underneath.[187] The critical electric field intensity (E_c) required to produce fibers from free-surface electrospinning was described as

$$E_c = \sqrt[4]{4\gamma\rho g/\epsilon_0^2} \tag{2}$$

where γ is the surface tension of the solution (N cm^{-1}), ρ is the density of the liquid mass (g cm^{-2}), g is the gravitational acceleration (cm s^{-2}), and ϵ_0 is the absolute permittivity (F cm^{-1}). During the onset of free-surface electrospinning, the electric force is essential for Taylor cone formation and subsequent jet initiation. Prior to jet growth and the corresponding bending instabilities, the initial straight segment of the jets is amplified as the Coulomb forces concentrate on the leading segments that are trying to reach the collector.[188] The ultra-slow-motion images presented in **Figure 10**d indicate the stages from Taylor cone

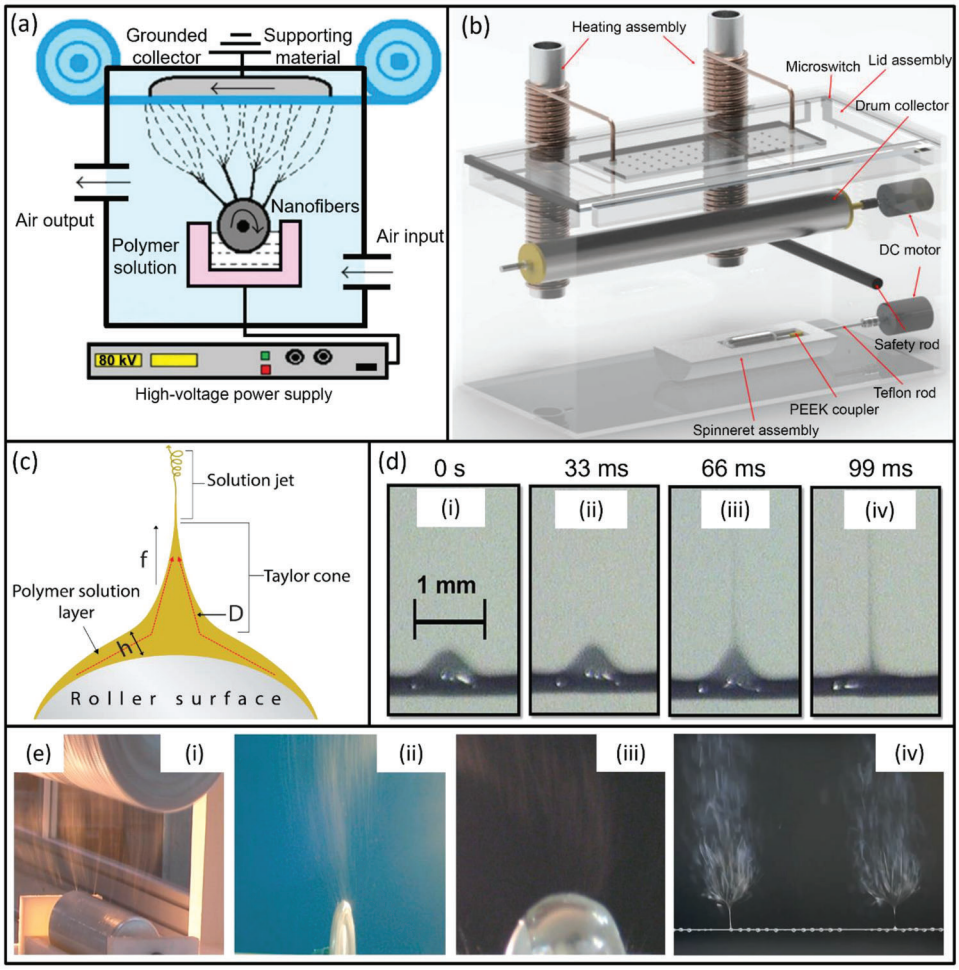

Figure 10. Roller and wire-based electrospinning. a) Diagram of a roller electrospinning setup. Modified from ref. [191]. b) Rendered CAD model of the nozzle-free roller electrospinning setup and its variant components. Retrieved from ref. [200]. c) Schematic diagram of Taylor cone formation via free-surface electrospinning. In the diagram, *h* represents the thickness of the layer, *D* the diameter covered by the Taylor cone, and *f* the electrostatic force. Adapted from ref. [200]. d) High-speed camera depicting jet formation: i) Conical droplet on an open surface in the presence of an electric field (time = 0 s), ii) extended conical droplet (time = 33 ms), iii) Taylor cone and jetting of the droplet (time = 66 ms), iv) depletion of the droplet (time = 99 ms). Adapted from ref. [201]. e) Photographs depicting multijetting based on various spinneret configurations: i) roller, ii) coil, iii) disc, and iv) wire. (i–iii) Reproduced from ref. [197]; (iv) Adapted from Nanospider (Elmarco, Ltd., Czech Republic). Copyrights: (a) Adapted with permission.[191] Copyright 2012, Hindawi; (b, c) Reproduced with permission.[200] Copyright 2021, Elsevier. (d) Adapted with permission.[201] Copyright 2012, American Chemical Society; (e) (i–iii) Reproduced with permission.[197] Copyright 2012, Taylor & Francis; (d) (iv) Reproduced from Elmarco, Ltd.

formation to jet depletion, which occur within a tenth of a second.

The section below discusses in detail the different forms of needleless electrospinning equipment that have been developed.

5.1. Free-Surface Roller and Wire-Based Electrospinning

Roller electrospinning is the first described needleless method capable of continuous fiber production. This method was invented by Jirsak et al., who first applied for a patent application in 2004 (application granted in 2009, US7585437B2).[24] Needleless roller electrospinning setups consist of a roller-spinneret electrode, a grounded or oppositely-charged rotating collector, a solution tank, a motor, and a high-voltage power supply (Figure 10 and **Table 11**).

During roller electrospinning, a rotating cylinder electrode (roller spinneret) is partially submerged in a polymer solution bath against a biased rotating collector electrode under constant airflow. Two motors control the rotating speed of the spinneret and collector cylinders. As the spinneret rotates, a fine layer of polymer forms at the upward-facing, non-submerged surface of the spinneret. A high-voltage power with a potential (generally greater than 50 kV) is then applied between the two rotating electrodes, inducing the formation of multiple Taylor cones emerging from the surface of the rotating electrode immersed in the solution bath.[189,190] When sufficient voltage is applied to the roller spinneret, the liquid layer electrifies, including multiple Taylor cones to formulate along the surface of the spinneret. When the voltage reaches a critical value, multiple jets stretch from numerous locations to form fibers in an upward motion on a large scale. Under a strong electric field, the jets are directed and deposited

Table 11. Advantages and disadvantages of free-surface roller and wire-based electrospinning.

Advantages	Disadvantages
1. Free-surface electrospinning based on the described configurations can attain high production rates through a continuous process, making it a viable approach for industrial production.[202]	1. The fiber diameters produced are usually larger than those produced by conventional electrospinning, while the process requires higher voltage for jetting.[191]
2. Increasing the polymer concentration increases productivity based on the weight of dry fibers collected.[203] Increasing the conductivity of the polymer solution will have a direct effect on the number of Taylor cones forming, and thus the incorporation of salts as additives is a common practice of further increasing fiber output.	2. Low controllability. Optimizing the parameters for consistency is much more complex than conventional electrospinning, primarily due to free-surface electrospinning being guided by random Taylor cone organization through the openly exposed polymer surface rather than a well-controlled individual Taylor cone in the case of needle-based electrospinning.[202] This, in most instances, is associated with much higher solvent and polymer wastage. Further optimization of the process should focus on reducing the proportion of un-spun polymer solution during the process.
3. Higher fiber production can be achieved while bypassing issues associated with nozzle-based setups, such as clogging and neighboring needle jet repulsion and deviation.	3. Difficulties obtaining consistent fibers and advanced fiber configurations, such as multicomponent composite structures. This is primarily due to the simple design of the spinneret and problems associated with solvent evaporation, and more strict solution requirements for successful electrospinning.[203]

on the collector's surface, which is placed at a fixed distance from the spinneret. Because of this, the roller electrospinning method is a continuous and efficient process for fabricating NFs.[191] Besides fluctuations in the conductivity of the polymer solution,[192] variations in the shape of the spinneret play a vital role in the morphology and diameter of the formed fibers.[193–196]

Generally, variations of the first described roller electrospinning method differ in the architecture and geometry of the free-surface spinneret. Within the roller electrospinning derivation, a roller can be in the shape of a cylinder, disc, or ball.[197] To better control the energy distribution, polymer layer thickness, and solvent exposure time, which are essential to obtain morphologically consistent fibers, spinnerets of wire and spiral configurations have been designed.[45] These were inspired by work conducted by Zhou et al. in 2014 that designed a spinneret consisting of two metal wires aligned parallel and near each other, capable of formulating compound Taylor cones out of polyacrylonitrile (PAN)/isophorone diisocyanate (IPDI), ultimately producing the first core/shell nozzle-less electrospun fibers at a high production rate.[198] At present, Nanospider (Elmarco, Ltd., Czech Republic) has developed a commercially available industrial-scale electrospinning device based upon this concept, where a high-voltage potential (up to 80 kV) facilitates the formation of fibers out of a polymer-layered thread at a defined rate. In recent years, the device has seen great commercial success through its production lines, Infinity and Linea, with research groups using it to report high-throughput fiber production.

Recent developments of free-surface apparatuses have successfully managed to produce binary and trinary composite fibers incorporating synthetic (PVP, polyglycerol sebacate [PGS], and PCL) and naturally derived (silk fibroin) polymers that presented improved surface chemistry, good adherence, and proliferation of fibroblasts in vitro and superior mechanical properties for skin tissue engineering applications. Earlier this year, a roller electrospinning setup was used to produce 3D electrospun PVDF polyvinylidene fluoride-*co*-trifluoroethylene (PVDF-TrFE) fibers presenting superior intrinsically enhanced piezoelectric properties through the integration of high-throughput produced NFs onto a mechanical energy harvester, obtaining a higher instantaneous output power than similar state-of-the-art devices.[199]

Although roller electrospinning presents a high-volume output and is easy to operate once the appropriate solution and electrospinning parameters have been established, it can be challenging to maintain consistent solution concentration and viscosity. Furthermore, due to the high electric force, incomplete solidification of the fibers can allow residual solvents to be incorporated into the scaffolds, which may affect the biocompatibility of the resulting constructs; nevertheless, postfabrication treatments may resolve this issue in most cases. In addition, a major concern is that as the polymer solution is openly exposed to ambient conditions, highly volatile solvents may rapidly evaporate, leading to fluctuations in the conductivity and viscosity that can negatively affect fiber uniformity and the consistency between experiments. This can be partially regulated by restraining the exposure of the polymer solution in the open air, the solvent system selection, regulating the ambient conditions, and the configuration of the spinneret (e.g., using a double-motion cartilage system to deposit the polymer solution and take up the excess polymer on the way back). Thus, it is necessary to accurately tune all solution, electrospinning, and ambient parameters to achieve a consistent fiber production output.

5.2. Bubble Electrospinning

Liu et al. invented bubble electrospinning in 2007.[39] As the name suggests, this innovative method facilitates free-surface jetting, out of an open polymer surface, by gassing a polymer solution, causing it to form polymer bubbles near the surface. The spontaneous formation of bubbles on the liquid surface reduces the surface tension of the electrospinnable solution, making it advantageous to other free-surface electrospinning configurations. Liu et al. showed that the process could yield ultrafine NFs at a 7.5 g h^{-1} production rate out of a single bubble by applying voltage ranging from 16 to 35 kV.[39] **Figure 11** illustrates a typical bubble electrospinning setup consisting of a solution reservoir

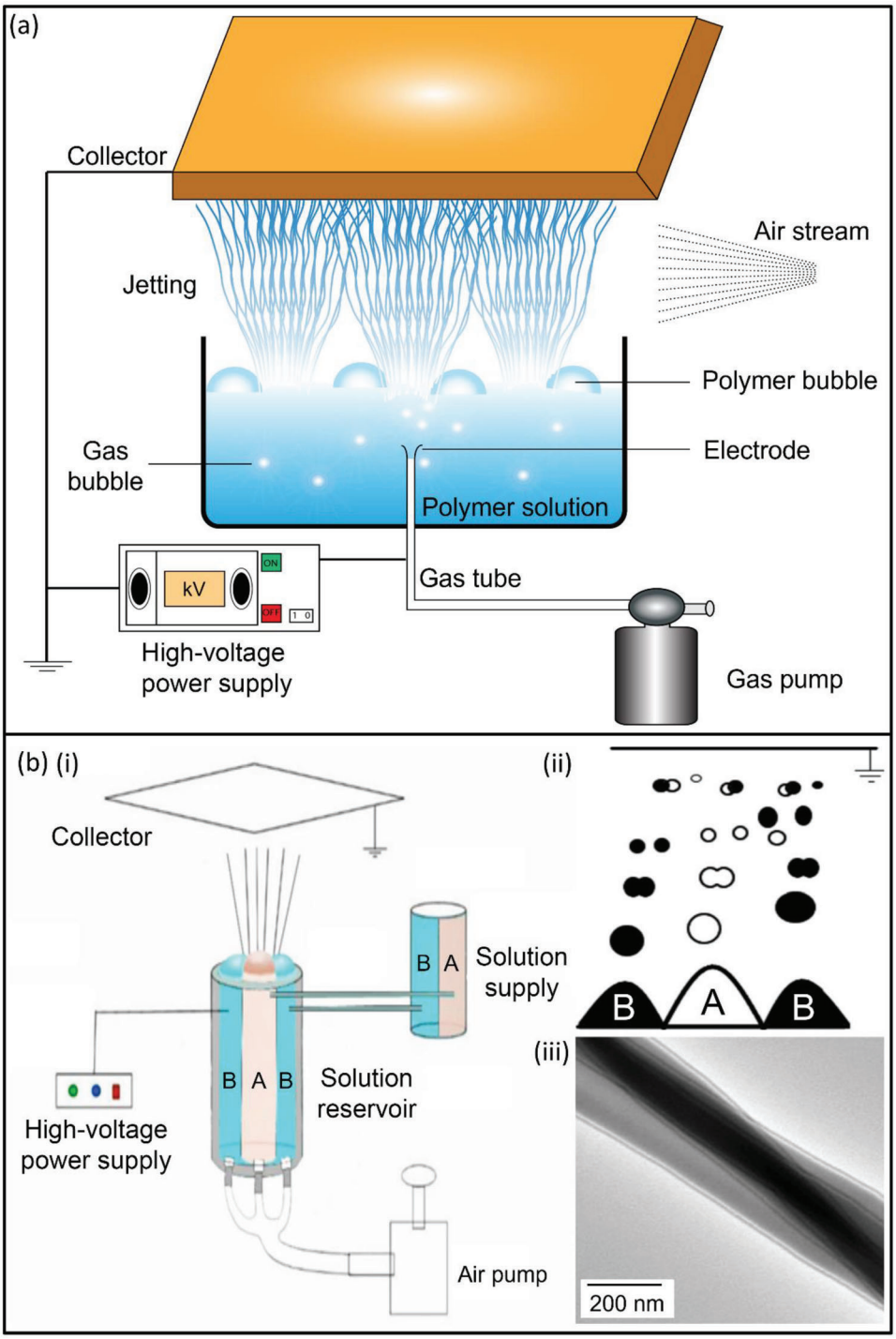

Figure 11. Bubble electrospinning. a) Schematic diagram of bubble electrospinning apparatus. b) A proposed method of producing core/shell NFs via co-axial bubble electrospinning; i) schematic of the process; ii) schematic of the mechanism depicting hybrid polymer bubbles forming at the surface between the two individual polymer solutions at the interface; iii) TEM image of the attained core/shell PVA and nylon-6 hybrid fiber structure. Adapted from ref. [204]. Adapted with permission.[204] Copyright 2021, Springer Nature.

Table 12. Advantages and disadvantages of bubble electrospinning.

Advantages	Disadvantages
1. It can be used for the mass production of NFs and scaled up for industrial applications.[39] This has been demonstrated by SNC Fibers (Stellenbosch, South Africa), which have employed bubble electrospinning for commercial production.	1. The constant evaporation of large amounts of solvent from the open surface area makes the process less safe for the operator and less environmentally friendly when harmful organic solvents are used for production.
2. Breakage of large bubbles and subsequent formation of daughter bubble cascades lowers the surface tension that must be overcome for Taylor cone formation, thus requiring lower working voltages compared to other high-throughput methods.[211]	2. The process is more susceptible to ambient conditions, with parameters surrounding the viscosity of the polymer solution and solvent volatility, rate of bubble formation (gas input), and electrospinning parameters requiring to remain at consistent levels to obtain homogenous reproducible fibers. These factors are affected by the pressure difference between the bubbles that have not reached the surface, and the external environment, which directs the surface tension of the bubbles.[39]

with a submerged gas tube and a metal electrode fixed at the bottom of the reservoir, a gas pump, a high-voltage power supply, and a collector plate (**Table 12**).

Initially, the reservoir is filled with the polymer solution. Gas pushed from the bottom of the polymer liquid generates bubbles at the reservoir's surface. This will incite air bubbles of assorted sizes to emerge from the bottom of the reservoir and rise to the surface of the aerated working solution. An electric field is applied by wiring the solution with high voltage, causing the meniscus bubble to rupture.[204] Upon rupture, microscopic charged droplets form at the surface, which due to electrostatic repulsion, become finer in size and break into smaller bubbles. The force induced by the surface is much greater at a smaller bubble radius.[204] Once the critical surface tension is overcome, the microbubbles at the solution's surface become unsteady, formulating individual Taylor cones. Once the electrical force overcomes the surface tension, a jet will be discharged from the conically shaped microbubble toward the grounded collector.

During bubble electrospinning, bubble collapse and wrinkle of the liquid sheet are responsible for Taylor cone formation and jetting.[205] Based on work by Oratis et al.[206] on bubble collapse dynamics that mathematically showed that surface tension drives bubble collapse and initiates wrinkle formation, earlier this year, He et al. used this principle to evaluate the maximal wrinkle angle for bubble electrospinning at 49°–50°.[207] It is worth mentioning that the threshold voltage needed to overcome surface tension is influenced by the size of the bubbles and the gas pressure inside them.

Bubble electrospinning has been successfully employed to electrospin a range of synthetic polymers. Li et al. have fabricated polymer blends of PVA, PVP, and PAN incorporating $ZrCl_2$ to produce high-temperature-resistant adsorption and separation membranes.[208] Liu et al. successfully produced PVDF/$FeCl_3 \cdot 6H_2O$ composite NFs, which were subsequently calcinated to create α-Fe_2O_3 NFs for catalysis.[209] Toward naturally derived polymers, Zhao et al. successfully electrospun silk fibroin/chitosan blends via bubble electrospinning.[210] Recently, Ali et al.[204] described the production of core/shell NFs via coaxial bubble electrospinning. The authors illustrated that it is feasible to attain composite core–sheath NF architecture via bubble electrospinning by incorporating two polymer reservoirs in a parallel configuration, as shown in Figure 11b, thus producing single polymer and hybrid fibers at the surface during the process. The mechanism is driven by a surface-induced force and geometrical potential. The authors theoretically and experimentally described that polymers mixed in a semi-solid state during the process could form an interface in a single fiber strand.[204] This exciting approach will require further characterization and optimization to facilitate the consistent production of core/shell NFs via this process rather than only a proportion of those present in the interface.

Among the several variations of open liquid electrospinning technologies, Korkjas et al.[99] recently developed a needleless ultrasound-enhanced electrospinning technique (USES) to generate multilayered nanofibrous membranes. USES generates an acoustic fountain by applying a high-intensity ultrasound to an electrified polymer solution instead of a gassing, depositing fibers in an upward motion. In this work, the conventional electrospinning parameters, along with the frequency and amplitude of the ultrasound signal generator, were appropriately adjusted to formulate bilayered PEO nanofibrous mats.

5.3. Corona Electrospinning

Corona electrospinning is an advanced high-throughput needleless electrospinning method patented by Molnár, Nagy, Marosi, and Meszaros in 2012.[202] Corona has benefits over other needleless apparatuses as the process works without an open liquid surface, with the solution flowing continuously through the unique architecture of the spinneret, significantly reducing problems associated with solution exposure. The setup consists of a corona spinneret, a high-voltage power supply, a circular electrode with a sharp edge, a grounded collector, and a feed supply unit. A schematic drawing of the procedure is depicted in **Figure 12** (**Table 13**).

The main working principle of this setup is to allow jets to generate from the edges of the circular electrode. The feed pump delivers the working fluid from the bottom to the top of the spinneret, and the polymer solution is continuously fed through a long, narrow gutter bound to a metallic electrode with sharp edges. Due to the rotating spinneret, the liquid is evenly dispersed and homogeneously distributed toward the edge of the circular electrode, forming cones and jets along the circular gutter. The sharp edge of the electrode contains the highest electrical

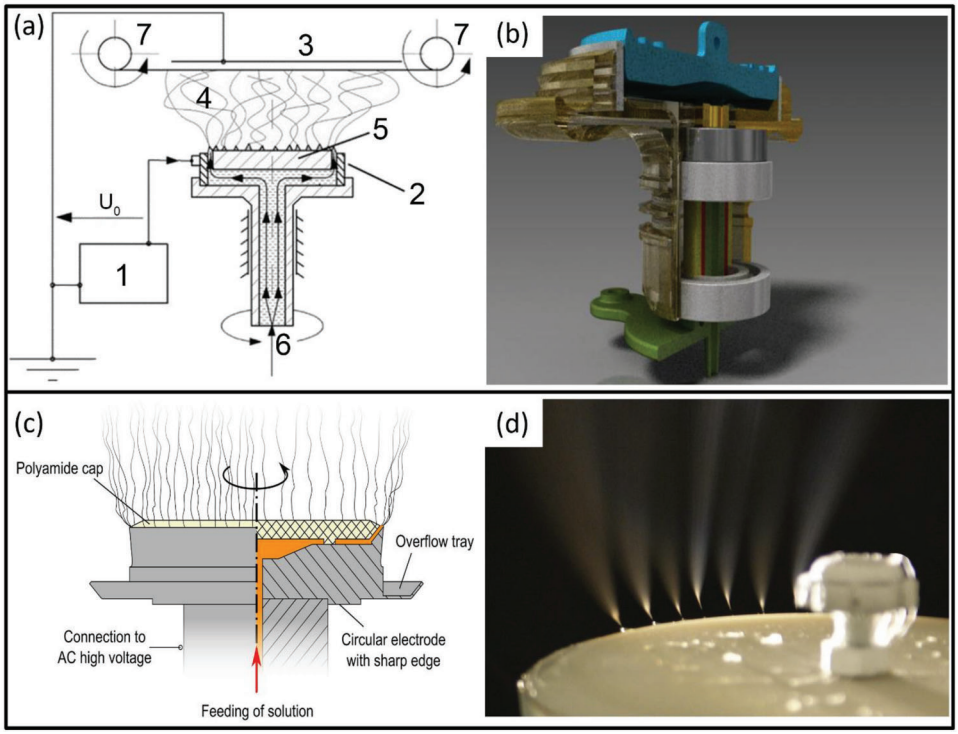

Figure 12. Corona electrospinning. a) Schematic diagram depicting the corona electrospinning process, with (1) high-voltage power supply, (2) circular electrode having a sharp edge, (3) grounded collector screen, (4) fiber formation space, (5) lid, (6) solution feed, and (7) traction of the collector textile. Reproduced from ref. [202]. b) CAD depicting the design concept of the spinneret. c) Schematic drawing of the C-ACES method coupled with AC high voltage. Reproduced from ref. [212]. d) Photograph indicating multiple Taylor cone formations along the edges of the 100 mm diameter spinneret. Reproduced from ref. [46]. Copyrights: (a, b) Reproduced from patent;[202] (c) Reproduced with permission.[212] Copyright 2019, Elsevier; (d) Reproduced with permission.[46] Copyright 2016, Elsevier.

Table 13. Advantages and disadvantages of corona electrospinning.

Advantages	Disadvantages
1. As it combines a nozzle-free spinneret configuration where fibers can be generated from its edges while the polymer solution is continuously fed into the system at a high flow rate, high-throughput production is achievable.[202]	1. To achieve high-throughput production,it is essential to rotate the spinneret at a certain speed to prevent overflowing and to match the flow rate of the polymer solution with the rotation speed of the spinneret.[46]
2. As the method does not constantly expose the polymer solution to an open surface, this method does not have an open liquid surface; it minimizes morphological inconsistencies due to solvent evaporation affecting the electrospinning process parameters. Therefore, it is possible to use volatile and low boiling point solvents to fabricate NFs, making it an especially interesting approach to producing NFs for pharmaceutical use.[46]	2. The process requires extremely high voltage (as high as 100 kV), which can increase the puchasing and operating costs of the power supplies and make the process less safe for the operator.[212]
3. The process can be more economical since there is minimal wastage; the entirety of the polymer solution added to the system can be electrospun. In contract, in free-surface setups, whatever is not electrospun must be discarded due to the exposure to ambient conditions.[46]	3. The process has not been extensively studied or replicated by other groups, with only four papers reporting the use of this technology on Scopus (Elsevier's abstract and citation database). Further research is required to optimize and reduce some processibility parameters (such as the high voltage) and to attempt to produce more intricate structures.

charge density, promoting the formation of Taylor cones, which allows many Taylor cones to self-assemble at the sharp edges of the spinneret simultaneously. When the electric field strength increases, multiple jets will eject from the tip of the Taylor cones. After solvent evaporation, fibers are collected in an upward motion. The initial prototype design of the spinneret reached production rates up to 300 mL h^{-1}.[46]

Recent work by Farkas et al.[212] has managed to further increase the production rate of the process, reaching 1200 mL h^{-1} via corona alternating current electrospinning (C-ACES), a variation of corona that combines the intense forces of an alternating electrostatic field with corona's sharp-edged spinneret configuration. The approach is conceptually similar to corona but uses an alternating current power supply rather than direct current

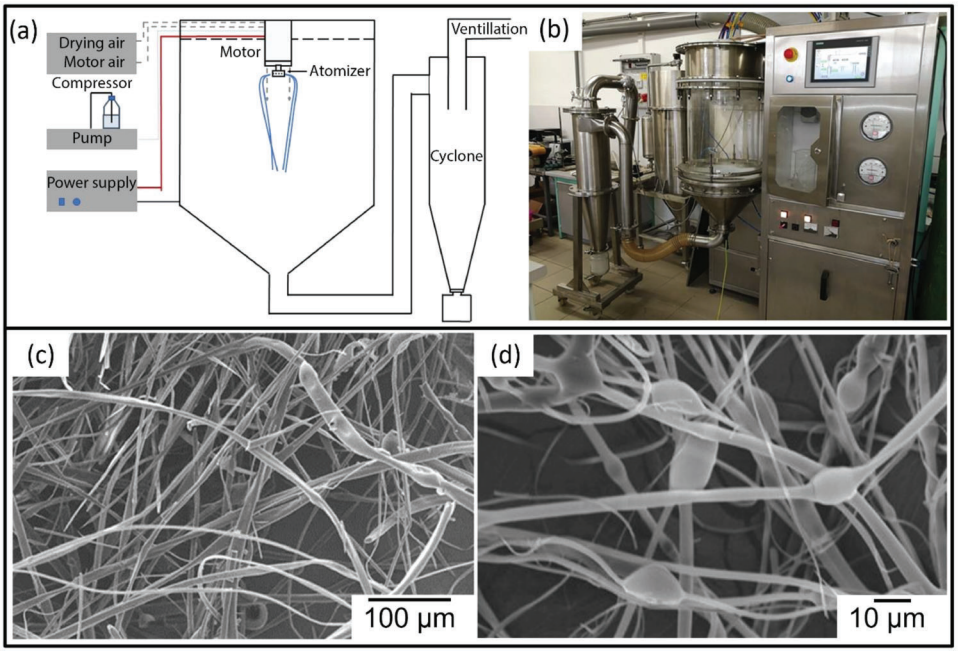

Figure 13. High-speed electrospinning. a) Schematic diagram of the high-speed electrospinning method. b) Photograph of the device with a continuous cyclone sample collector. Reproduced from ref. [213]. SEM images of c) β-galactosidase containing 2-hydroxypropyl-beta-cyclodextrin-based fibers and d) Kollidon VA 64 loaded with itraconazole. Reproduced from refs. [213] and [49], respectively. Copyrights: (a, b) Reproduced with permission.[213] Copyright 2015, Elsevier; (c, d) Reproduced with permission.[49] Copyright 2020, Elsevier.

Table 14. Advantages and disadvantages of high-speed electrospinning.

Advantages	Disadvantages
1. Capable of continuous production of large quantities of fibers at a fiber output of 450 g h^{-1}.	1. This process cannot produce complex structures (e.g., core–shell).
2. As the process does not present a free liquid surface, it can be used with volatile and low boiling point solvents, similar to corona electrospinning.	2. The process requires an extremely high rotational speed and high voltage. The fibers produced via this process present secondary morphologies (e.g., beads) and lack homogeneity with a large standard deviation in fiber diameter.
3. Fibers are collected in a cyclone rather than a collector, a new approach that can produce fragmented fibers, which helps their downstream processing for pharmaceutical applications.	3. More research is required to evaluate this relatively new process's advantages and limitations and better understand the processing parameters.

high voltage. During electrospinning, the authors used an annular orifice spinneret 110 nm in diameter, rotating at 100 rpm, applying a 100 kV voltage at a 50 Hz frequency at a feeding rate ranging from 100 to 1200 mL h^{-1}, collecting fibers in an upward motion from a 75 cm distance (between the spinneret and the collector's surface). The authors employed this technique to produce PVP K90 NFs loaded with spironolactone (an aldosterone receptor antagonist).[212]

5.4. High-Speed Electrospinning

In 2015, Nagy et al. first described high-speed electrospinning to produce co-polyvidone (Kollidon VA 64) NFs loaded with a poorly water-soluble antifungal drug, itraconazole.[49] High-speed electrospinning combines electrostatic and high-speed rotational jet generation and fiber elongation resulting in a significant increase in fiber production output.[213]

The setup (**Figure 13** and **Table 14**) consists of a stainless-steel disc-shaped spinneret equipped with 36 equidistantly distributed orifices on the wheel's side wall. The spinneret rotates via a high-speed motor. The rotational speed of the spinneret can be increased up to 50 000 rpm. This high-speed rotation exerts a centrifugal force on the solution, which is forced through the orifices of the spinneret, allowing the jet formation to occur in the presence of a high voltage (greater than 40 kV). The fibers are collected within a cyclone rather than a collector surface after jetting. This way, no free liquid surface is present, and solvent evaporation from the solution is minimized before fiber formation starts, which helps maintain the solution's concentration and viscosity during the electrospinning process. Using this method, the authors evaluated the production rate at ≈450 g h^{-1} (at a feeding rate of 1500 mL h^{-1}), with the possibility of each electrospinning reactor producing about 10.8 kg d^{-1}.[213] Such a scaled-up, continuous, flexible manufacturing process

can meet the capacity requirements of the pharmaceutical industry.

6. Comparison of Different Methods

Table 15 comparatively summarizes the key advantages and disadvantages of the different electrospinning techniques.

7. Discussion and Limitations

Despite the apparent advantages and broader applicability of electrospun fibers over other fiber preparation techniques, as shown in Table 15 above, each and every one of the electrospinning methods described in this review carries its limitations.

The most recognized limitation of conventional electrospinning is the low production rate and the fact that not all materials are appropriate for electrospinning. For example, because of their low molecular weights, many conductive polymers have relatively low solubility in commonly used solvents. They lack enough chain entanglement to maintain stability. Additionally, due to their highly conductive nature, forming a steady jet is challenging. Therefore, electrospinning them into fibers is challenging. A commonly used approach is mixing them with other electrospinnable polymers. However, in this instance, the compatibility of the two materials should be taken into consideration.

When it comes to tissue engineering, one of the main concerns with conventional electrospinning is the limited cell infiltration into the electrospun scaffolds and restricted tissue ingrowth due to their highly dense 2D structure and small diameter pores. The compact and superficial porous structures of these scaffolds result in low cell penetration. The high porosity and small pore size associated with conventional electrospun fibers are directed by the diameter of the fibers and fiber interconnectivity. This phenomenon becomes more pronounced as the diameter of the NFs decreases. While the inherently porous structure of electrospun scaffolds provides fenestrations that are insufficient for most cell types to pass through, they are sufficient for nutrient and cytokine transport. Whilst cellular expansion in the form of a monolayer is not problematic for the development of wound dressings, as the construct is merely meant to facilitate cell migration and proliferation, 3D structures can further enhance fluid retention and exudate absorption. Further research in post-fabrication technologies such as freeze-drying and gas-foaming to expand the scaffold's 2D structure or advancements in technologies such as 3D electrospinning can, in due course, resolve these issues.

The possibility of residual toxic chemicals remaining within electrospun fibers is another limiting factor. The properties of the selected solvent are a critical electrospinning parameter, as it can determine whether a specific polymer can be electrospun and directly affect the morphology of the produced fibers . Highly volatile solvents are generally used in electrospinning to produce dry fibers. However, in a some cases, residuals remain on the surface of the electrospun fibers, which could lead in cytotoxicity when the fibers are used in medical and pharmaceutical applications. Moreover, many postprocessing procedures rely on harsh substances that can pass through to the final product. The use of organic solvents for electrospinning requires further investigation into the use of green solvents when considering the significant amounts of solvent needed for electrospinning and their negative environmental and health impact.

Co-axial and multi-axial electrospinning present similar limitations. The principal constraint of the process is that all the polymer solutions used must be compatible; otherwise, electrical forces cannot draw them together without coagulation. To ensure the development of a compound Taylor cone at the tip of the spinneret, it is essential to maintain its concentric structure throughout the jet expansion and for the entire process duration. The second limiting factor is that each solution must present similar physicochemical properties. A suitable viscous force is needed to maintain the Taylor cone and prevent its separation during the bending instabilities stages of jetting. This is a valid concern when one of the solutions dries faster than the other. When the working solutions are compatible, the co-axial and triaxial electrospinning methods tend to be successful upon appropriate parametric assessment. The third limiting factor is the balance between the flow rates of different solutions. Variations in the flow rate will affect the final compound fiber quality. A low flow rate would disrupt fiber formation, while a high flow rate would break the structure. Finally, the fourth limiting factor is the design of the complicated concentric spinneret, which plays an essential role in this method. The spinneret provides a suitable working environment for attaining NF of the desired configuration, and it can positively or negatively influence the composite droplet's behavior under the electric field.

3D electrospinning is the only reported technology capable of producing 3D microstructures in the micro/nanoscale in a single-step process—3D electrospinning benefits from unifying a fused deposition modeling 3D printing architecture with electrospinning. The technology has been successfully employed to produce woven electrospun structures by directing the deposition of the fibers via a Cartesian coordinate system. As a relatively new fabrication approach, research should focus on building more mechanically stable structures. Although cryo-electrospinning and wet electrospinning can produce non-woven randomly oriented 3D structures, both processes are limited to the availability of compatible polymer–solvent systems and, in most instances, require post-fabrication processing to obtain the final 3D form.

Portable electrospinning is a fascinating technology that illustrates the feasibility of electrospinning using a battery-powered handheld apparatus, producing NFs at a lower voltage in an in situ manner. This technology has potential in wound healing management, as it allows for the direct deposition of fine fibrous layers in open wounds, which can protect the wound bed from infection and promote healing while reducing patient discomfort. Although the process has been successfully used to incorporate pharmaceutical compounds into a range of synthetic polymers and a clinical trial assessing the effect of portable electrospinning in wound healing is ongoing, further research is needed to address operational safety concerns, solvent limitations (due to residual solvents) and the stability of the process toward fiber morphology.

The primary limitation of the needleless electrospinning techniques is mainly related to the relatively sizeable free liquid surface exposure during the process. Bubble electrospinning, in particular, has immense free liquid surface exposure due to bubbling. Alongside the formation of polymer jets, solvent evaporation can be detrimental to the surrounding environment and

Table 15. Comparison of different methods based on the advantages and disadvantages.

	Electrospinning technique	Advantages	Disadvantages
Needle-based	Mono-axial	1) Well-studied, simple setup, easy to operate. 2) An easy way to evaluate the electrospinnability of new materials and optimize parameters. 3) Morphologically consistent NFs can be produced. 4) Composite fibers can be developed via blending.	1) Low productivity. 2) Simple fiber architecture (monolithic). 3) Single fiber configuration. 4) Compact 2D structure of high density and small pore size.
	Co-axial	1) Creates novel core–shell or hollow structures. 2) Tune (drug) release profiles. 3) Can produce NFs from otherwise unspinnable materials.	1) Low productivity. 2) Relatively complicated spinneret. 3) Difficult to implement and balance the flow rates of different fluids in a composite jet.
	Tri-axial	1) Creates a novel trilayer structure. 2) Can produce composite fibers of enhanced mechanical stability and biocompatibility (e.g., incorporating synthetic polymers in the multiple cores and naturally derived material in the sheath). 3) Can produce complex drug-release systems. 4) Can produce NFs from unspinnable materials.	1) Low productivity. 2) Complicated spinneret structure. 3) Difficult to implement and balance the flow rates of different fluids in a composite jet. 4) Arduous and time-consuming process of cleaning the spinneret. Taylor cone stability requires constant supervision.
	Centrifugal	1) Can obtain homogenous NFs of variant diameters. 2) Produces loosely packed microfibrous structures that can enable better cell infiltration. 3) Combines the advantages of traditional electrospinning and centrifugal spinning techniques. 4) Can be scaled up.	1) A relatively new method that requires further investigation of the parameters influencing the process. 2) Single fibers with simple structure. Only a few recent papers have focused on attaining core/shell fibers. 3) Nozzle clogging and unconventional collector configurations.
	3D	1) The only single-step method capable of producing 3D fibrous structures. 2) Woven or nonwoven structures are obtainable with processes such as 3D electrospinning or cryo-electrospinning, respectively. 3) The shape and macromorphology of the 3D structure can be directed.	1) Relatively new method. 2) Polymer systems with higher conductivity are necessary for 3D assembly. 3) Increasing the height of the 3D structure reduces the precision of the process. 4) Poor mechanical stability.
	Portable	1) The only method capable of in situ electrospinning. 2) Mostly applicable for wound healing, with the potential of being used for on-site wound management. 3) Cordless, handled electrospinning setup powered by a battery. 4) Can incorporate pharmaceutical compounds or other active substances and nanomaterials (e.g., nanoparticles).	1) Extremely new technology. 2) Poor stability during electrospinning and safety concerns (e.g., residual solvents). 3) Predominately used with water and ethanol-soluble polymers; issues associated with solvent evaporation need to be addressed.
Needleless	Roller	1) High-throughput production of micro/nanostructured fibers. 2) Continuous fabrication can be implemnted for industrial-level production. 3) Easy to manipulate the production rate and fiber diameter. 4) The most researched needleless method in the literature.	1) Predominately produces large fiber diameters of a high standard deviation and less morphologically consistent fibers than needle-based setups. 2) Requires a higher voltage to initiate jetting compared to needle-based setups. 3) Susceptible to ambient conditions; solvent volatility due to the exposed open surface, which can affect fiber homogeneity.
	Bubble	1) High production rates are attainable; it has been successfully employed for mass production. 2) Can be operated with a low voltage compared to other needleless methods.	1) A newly described and not yet thoroughly researched technology. 2) The large exposed area poses safety issues for the operator and environment when toxic solvents are used. 3) Susceptible to ambient conditions and air pressure, reduces fiber homogeneity when electrospinning is prolongated.
	Corona	1) Low-free liquid surface spinneret. 2) Continuous high-throughput fabrication is feasible. 3) Unique spinneret architecture allows polymer solution shielding while instantaneously promoting high-throughput electrospinning.	1) Requires a certain rotating speed to avoid overflow. 2) Requires extremely high voltage. 3) A relatively new process needing further research to understand its advantages and limitations.
	High-speed	1) High productivity (≈0.5 kg h^{-1}). 2) Continuous fiber production is possible. 3) Fiber fragmentation in the collector cyclone can help downstream processing.	1) Production of complex fiber structures (core–shell) is not possible. 2) Process requires extremely high rotational speed and high voltage. 3) A relatively new process requiring further research to understand its advantages and limitations.

harmful to the operator. In extreme cases, when the concentration of the combustible solvent accumulates to a critical value, it will cause ignition. Another concern is that a large liquid surface enhances water absorption from the air, diluting the spinning solutions and thus affecting fiber consistency and quality. In addition, needleless electrospinning technologies are overall associated with poorer fiber homogeneity and reduced consistency among batches. The higher critical potential required to attain Taylor cone formation in needleless electrospinning methods often limits the selection of polymers that can be electrospun, and the complexity of the polymer system. Thus, these techniques have limitations in polymer selection, operating costs, and environmental concerns. Additionally, it will be a long time before needleless electrospinning methods can fabricate NFs with complex structures such as side-by-side and core–sheath cross-section configurations.

Many approaches have been considered to overcome the problems associated with fiber quality and reproducibility when using needleless setups. First, needleless setups can be enclosed in sealed transparent containers to reduce solvent evaporation. The humidity inside the container can be controlled to prevent significant water absorption from the air. Second, by modifying the design of the spinneret and optimizing process parameters, the ejecting speed and jetting can be accurately manipulated. Finally, developing spinneret configurations that limit polymer exposure while retaining a high surface electrode area for high-throughput production is an effective way of improving consistency.

8. Future Perspectives

Although it is easy to recognize that electrospinning is a fascinating technique for fabricating a large variety of intriguing micro and nanoscaled materials, potential problems still need to be addressed.

A small proportion of the research has focused on modeling; however, a universally accepted simulation model for accurately predicting the needle-based or needleless electrospinning parameters has not yet been developed. As a result, the majority of electrospinning experiments rely on an empirical understanding of the process requirements and parametric studies. For instance, in needleless electrospinning, the challenge remains in producing uniform fibers with high output while simultaneously obtaining the desired fiber diameter, structure, and application-specific properties . To overcome these limitations, researchers should be more open to sharing positive and negative results on optimizing the different parameters of the techniques, including solution, process, and ambient conditions. This approach will help to better understand and control the morphology and reproducibility of each technology. This progress will help better predict the Taylor cone formation requirements, jet behavior, and fiber output.

Another critical concern is the economic and environmental aspects of the processes. Over the years, many solvents have been successfully used to produce electrospun fibers through solution electrospinning. However, the predominant number of solvents used to formulate fibers today can significantly impact the environment and human health by being harmful to humans and ecosystems. This is especially true for needleless electrospinning since it has a large liquid surface exposed to the air, and highly volatile solvents are evaporated into the surrounding environment. This is not ideal for the mass production of fibers in the industry. Although a significant amount of work has been carried out using aqueous polymeric solutions as a less harsh alternative to organic solvents, when the processibility of the polymer in water is not feasible, directing the focus toward the use of "green" solvents is essential. Although using melt electrospinning seems like a simple approach to meet these requirements, the process has limitations concerning the complexity of the fibers produced, producing fibers large in diameter, polymer-related thermal degradation, and incompatibility with several high-throughput technologies discussed in this review.

9. Conclusion

It is universally acknowledged that electrospinning has played a significant role over the past two decades in developing diverse advanced nanostructured materials for almost every conceivable application. Researchers from around the globe have contributed to the evolution of the electrospinning principles, uncovering the process's capabilities and discovering technologies and methods to move forward and push the limits of this technology. Significant progress has been made in understanding its principles and exploring its applications, as has been documented by the exponential and consistent increase in the number of publications and patents filled in the past two decades.

This review focused on comparing the advantages and limitations of needle-based and needleless electrospinning technologies. A brief history and background knowledge of the electrospinning principles were highlighted. Generally, the fundamental problem associated with needle-based techniques is scaling up limitations and operational complexities. For needleless processes, on the other hand, the critical issues are related to the large free liquid surface, which results in economic and environmental issues and difficulties in obtaining morphologically consistent batches between experiments. Many parameters of newly invented techniques still need to be optimized.

The future of each technology and its advancement or dismissal will depend on specific application requirements, including specialized structures, multifunctional hierarchical organizations, and scaling for industrial production. The combination of electrospinning with other fabrication methods (e.g., bioprinting) holds a promising future for numerous applications.

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Conflict of Interest

The authors declare no conflicts of interest.

Keywords

3D electrospinning, advanced fibers, corona, electrospinning, needleless

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