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ADVANCED REVIEW

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Scale-up of electrospinning technology: Applications in the pharmaceutical industry

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Abstract

Recently, electrospinning (ES) of fibers has been shown to be an attractive strategy for drug delivery. One of the main features of ES is that a wide variety of drugs can be loaded into the fibers to improve their bioavailability, to enhance dissolution, or to achieve controlled release. Besides, ES is a continuous technology with low energy consumption, which can make it a very economic production alternative to the widely used freeze drying and spray drying. However, the low production rate of laboratory-scaled ES has limited the industrial application of the technology so far. This article covers the various ES technologies developed for scaled-up fiber production with an emphasis on pharmaceutically relevant examples. The methods used for increasing the productivity are complied, which is followed by a review of specific examples from literature where these technologies are utilized to produce oral drug delivery systems. The different technologies are compared in terms of their basic principles, advantages, and limitations. Finally, the different downstream processing options to prepare tablets or capsules containing the electrospun drug are covered as well.

This article is categorized under:
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KEYWORDS

amorphous solid dispersion, continuous pharmaceutical manufacturing, electrospinning, oral drug delivery, scale-up

1 | INTRODUCTION—EARLY PIONEERS IN THE ELECTROSPUN ORAL DRUG DELIVERY SYSTEMS

Electrospinning (ES) was originally reported in 1899 and the technology has been used since for the fabrication of continuous fibers (Cooley, 1899). Beginning from the 1980s and particularly during the recent decade, the technology has gained increasing attention. Possibly this can be attributed to the surging interest in nanotechnology, as ultrafine

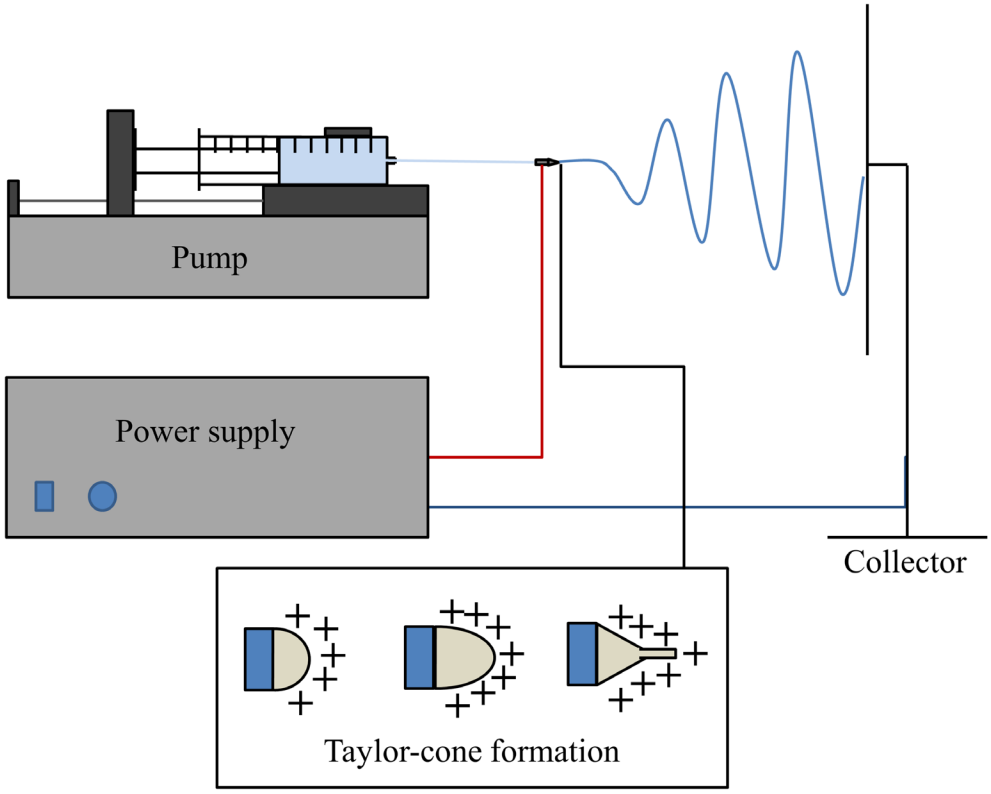

FIGURE 1 Schematic drawing of single-needle electrospinning (SNES)

micro- or nanofibers or fibrous structures of various polymers or cyclodextrins can easily be fabricated using this process. The applications of electrospun products are expanding, especially in areas relating to drug delivery and tissue engineering (Hu et al., 2014; Sill & von Recum, 2008; Thakkar & Misra, 2017).

Electrospinning is a low-cost technology to generate dried fibers by utilizing the electrostatic forces on a liquid feed to turn it into ultrafine (normally <10 μm; Cramariuc et al., 2013) fiber structures, which can dry instantly at room temperature during process operation. The basic technology is called single-needle ES (SNES; Figure 1), during which the fiber-forming excipient (polymer or cyclodextrin, lipid, etc.) is dissolved in a solvent and the solution is fed into a single spinneret at a constant, controlled flow rate. High voltage is applied between the spinneret and the grounded collector, which causes the formation of a Taylor cone. If the electrostatic forces overcome the surface tension, a liquid jet breaks out from the cone (Taylor, 1964) and stabilizes between the nozzle and the collector as a continuous stream. During the process, the jets get elongated gaining a fiber-like structure, and the solvent evaporates instantaneously due to the high surface area, as the fibers are often submicron-sized.

During the last decades, electrospun fibers have become attractive oral drug delivery systems, mostly because they can improve the absorption of poorly soluble drugs by enhancing the dissolution rate of drug molecules through amorphization. The very efficient amorphization effect of ES is due to the immediate evaporation of the solvent, which results in solid solution of the drug in the applied matrix (Begum et al., 2012; Nagy et al., 2012; Vigh et al., 2013; Vrbata, Berka, Stránská, Doležal, & Lázníček, 2014). Electrospun fiber-based amorphous solid dispersions are able to maintain an incorporated active ingredient in the amorphous physical form for prolonged periods of time because of their homogeneous drug distribution within the matrix and ability to inhibit molecular motion (Yu, Li, Williams, & Zhao, 2018). Additionally, sustained supersaturation can be achieved, resulting in an increased driving force for absorption (Borbás et al., 2016). The first patent about electrospun oral drug delivery systems contained a very comprehensive description of the technology and was submitted by Ignatious and Baldoni in 1999 (Ignatious & Baldoni, 2001). In 2003, the first scientific article was published by Verreck et al. about dissolution enhancement for oral drug delivery using electrospun nanofibers (Verreck, Chun, Peeters, Rosenblatt, & Brewster, 2003). In this pioneer work, itraconazole-loaded hydroxypropyl methylcellulose (HPMC) fibers were produced and the dissolution rate of the poorly water-soluble itraconazole was increased significantly. A few years later, in 2009, Yu et al. published a polyvinylpyrrolidone-based oral fast-dissolving drug delivery system (Yu et al., 2009), in which 85% drug release was achieved in the first 20 s of

dissolution. In 2010, 100% drug release was reached within a few seconds using a polyvinyl alcohol-based orally dissolving web (Nagy, Nyul, Wagner, Molnar, & Marosi, 2010). From 2010, the number of publications aiming at oral drug delivery using electrospun fibers increased exponentially (Ignatious, Sun, Lee, & Baldoni, 2010; Yu et al., 2018).

Most of the publications, however, employ SNES having rather low productivity (<1 g/hr), which does not satisfy the needs of the pharmaceutical industry. Therefore, multiple attempts were made for the scale-up of the technology to reach production rates sufficiently high for industrial applications (Mehta et al., 2017). Besides increased productivity, current development needs to focus on fiber collection methods and the downstream processing of the produced fibers as well.

This review aims to give an overview of the ES technologies developed for scaled-up fiber production with an emphasis on pharmaceutically relevant examples. First, different methods to increase fiber production are discussed in terms of their basic principles, advantages, and limitations. This is followed by examples from literature about the scaled-up production and downstream processing of drug-containing fibers produced for oral drug delivery.

2 | SCALED-UP ES TECHNOLOGIES

This paragraph is a general overview of the different ways of increasing the output of ES. The productivity of the simplest ES method is usually around 0.01–1 g/hr, falling short of the requirements of clinical and commercial industrial production. Therefore, technological changes are needed for raising the output of ES. The scale-up of ES technology is based on increasing the number of Taylor cones, which means increasing the number of liquid jets leaving the solution. Basically, the modified ES techniques can be divided into two main groups according to their working principle: nozzle and free surface methods (SalehHudin, Mohamad, Mahadi, & Muhammad Afifi, 2018). The nozzle ES apparatuses are systems with limited open solution surface, where the solution is being fed directly into the charged needles or multiple-hole spinnerets. In contrast, significantly more Taylor cones can be formed during free surface ES methods, during which many liquid jets are able to leave from the open surface of the solution. Furthermore, both groups consist of some subgroups (depending on the type of the spinneret), which include several high-performance ES methods (Tables 1 and 2; Yan, Niu, & Lin, 2019; Yu et al., 2017).

2.1 | Nozzle-type technologies

Among nozzle-type techniques (summarized in Figure 2 and Table 1), *multi-needle ES* is considered to be the easiest solution to increase productivity, when the arrangement and the distance of the two or more needles can be multifarious (Figure 2a,b; Cabello et al., 2017; Zhou, Gong, & Porat, 2009b). The main challenge of these methods is to avoid the interaction of the electrostatic fields formed by the needles carrying the static charge. As a result of interaction, repulsive forces may occur between the liquid jets, which can lead to increased variation of fiber quality. The application of *tubular* (Figure 2c) or *flat spinnerets* (Figure 2d) with holes reduces the interaction between the leaving jets (Teo, Kotaki, Mo, & Ramakrishna, 2005; Zhou et al., 2009a). However, no notable increase in productivity has been reported using multiple needles, and presumably it is the reason why these methods did not spread in practical usage. Much higher production rates can be achieved with *electroblowing* (Figure 2e) when an additional air flow facilitates the solvent evaporation

TABLE 1 Summary of nozzle-type electrospinning scale-up methods—Schematic drawings of the different methods can be found in Figure 2

Nozzle electrospinning			
Type of spinneret	Method	Productivity (g/hr)	Reference
Stationary	Multi-needle (linear or two-dimensional arrays)	0.1–1/needle	Cabello, Sandoval, Rovira, and Rubio (2017); Theron, Yarin, Zussman, and Kroll (2005)
	Porous tube	0.3–0.5	Varabhas, Chase, and Reneker (2008)
	Flat spinneret	1.68	Zhou, Gong, and Porat (2009a)
	Electroblowing	42.5–56.7	Sóti et al. (2015)
Rotary	Nozzle-based high-speed	240	Vass et al. (2019)

TABLE 2 Summary of free surface electrospinning scale-up methods—Schematic drawing of the different methods can be found in Figure 3 and 4

Free surface electrospinning			
Type of spinneret	Method	Productivity (g/hr)	Reference
Stationary	Wire	27	El-Newehy, Al-Deyab, Kenawy, and Abdel-Megeed (2011)
	Conical wire	0.86–2.75	Wang, Niu, Lin, and Wang (2009)
	Bowl	0.684	Thoppey, Bochinski, Clarke, and Gorga (2011)
	Plate edge	0.27	Thoppey, Bochinski, Clarke, and Gorga (2010)
	Curved slot	0.6	Yan et al. (2017)
	Slit	0.9	Pham et al. (2013); Sharma, Pham, Marini, Yan, and Core (2014); Yan et al. (2015)
	Stepped pyramid	2.3–5.7	Jiang, Zhang, and Qin (2013)
Moving	Magnetic fluid	12	Yarin and Zussman (2004)
	Bubble	2.352	Liu, He, and Yu (2008)
	Ball	3.1	Miloh, Spivak, and Yarin (2009); Smit and Sanderson (2009a) and (2009b)
	Rotary disk	6.2	Niu, Lin, and Wang (2009)
	Cylinder	8.6	Sutka, Kukle, Gravitis, Milašius, and Malašauskienė (2013)
	Beaded-chain	40	Liu et al. (2014)
	Rotary wire	0.05/wire	Forward, Flores, and Rutledge (2013); Forward and Rutledge (2012) and (2013)
	Spiral coil	2.94–9.42	Wang, Niu, Wang, and Lin (2012)
	Corona	60	Molnar and Nagy (2016)
	Free surface high-speed	450	Nagy et al. (2015)

(Armantrout, Bryner, & Spiers, 2009; Balogh et al., 2015; Kakoria & Sinha-Ray, 2018; Medeiros, Glenn, Klamczynski, Orts, & Mattoso, 2009; Pokorny, Rassushin, Wolfova, & Velebny, 2016; Sóti et al., 2015). Although the feeding rate is increased during the electroblowing process, beads or droplets can also appear among the fibers more frequently due to the effects of the air flow. In addition, the main limitation of all nozzle techniques is the possibility of spinneret clogging, and therefore, adjusting the process parameters (feeding rate, applied voltage, etc.) requires thorough optimization.

The application of *rotating spinnerets* can reduce the likelihood of clogging due to the centrifugal force that pushes the solution through the nozzle. The possibility of clogging can be reduced even further if the spinneret contains orifices instead of needles. In addition, the liquid jet is continuously stretched and elongated by the centrifugal force and therefore it is possible to use rotating spinnerets to prepare fibers (Hooper, 1922; Huttunen & Kellomäki, 2011; Weitz, Harnau, Rauschenbach, Burghard, & Kern, 2008) with increased yields even without applying voltage. Sarkar et al. developed the Forcespinning® technology and increased production rates were reported in the case of polypropylene (PP), polylactic acid, polycarbonate, acrylonitrile butadiene styrene, and polyethylene oxide using 3,000–5,000 rpm rotational speed (Lozano & Sarkar, 2009; Padron, Fuentes, Caruntu, & Lozano, 2013; Sarkar et al., 2010). The pressurized gyration technique is another voltage-free fiber production method utilizing a small cylindrical vessel with multiple orifices (Mahalingam & Edirisinghe, 2013). The vessel is connected to a motor (capable of rotational speeds up to 36,000 rpm) and a gas inlet (gas pressure up to 0.3 MPa). The solution is loaded into the vessel and fiber formation is induced by the combined application of the rotation and gas pressure. This setup was shown to be capable of spinning 5 ml of solution in less than 15 s; however, the continuous operation of pressurized gyration technology has not been presented yet and the volume of the applied vessel is the limiting factor of the productivity (Heseltine, Ahmed, & Edirisinghe, 2018). Sebe et al. developed high-speed rotary spinning employing a rotating reservoir (80 mL) with nozzles that can be spun at 3,500 to 10,500 rpm. They reported a productivity rate similar to the Forcespinning® technology (around 60 g/hr; Sebe et al., 2013; Szabó, Kállai-Szabó, Kállai-Szabó, Sebe, & Zelkó, 2014). However, all the technologies above do not utilize and benefit from electrostatic forces and therefore they cannot be considered ES methods.

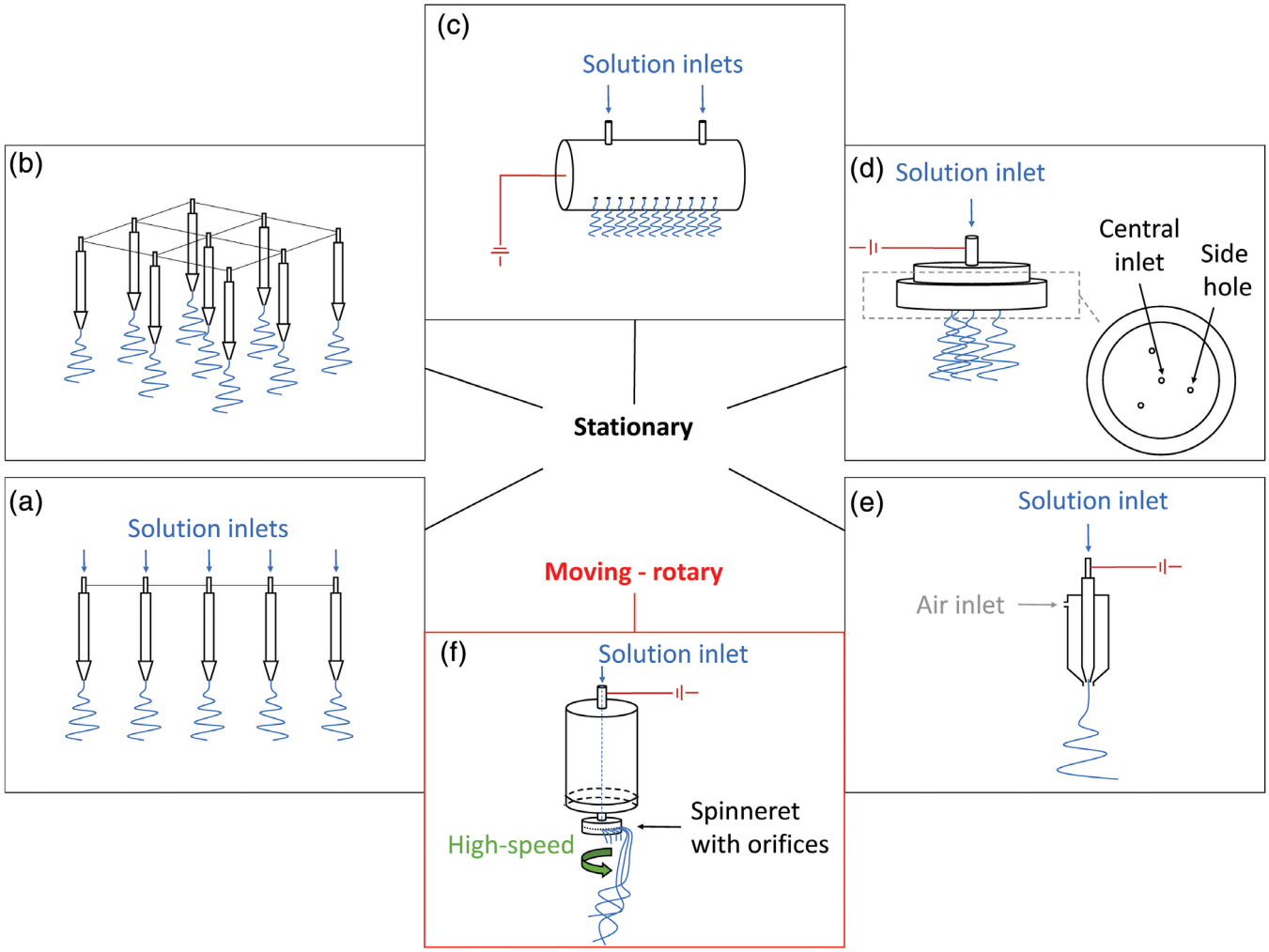

FIGURE 2 Nozzle-type electrospinning spinnerets, (a) linear multi-needle; (b) two-dimensional multi-needle; (c) porous tube; (d) flat; (e) electroblowing; (f) nozzle-based high-speed

Recently nozzle-based high-speed ES (Figure 2f) was created, which combines high voltage and a rotating spinneret with orifices. The technology can be operated at 40,000 rpm rotational speed and it exploits both centrifugal and electrostatic forces to form fibers with up to 240 g/hr productivity (Vass, Démuth, Farkas, et al., 2019).

2.2 | Free surface technologies

The abovementioned spinneret clogging can be avoided using free surface ES (summarized in Figures 3 and 4, and Table 2), since the curvature formation of the liquid surface makes the fiber production possible without nozzles (Niu & Lin, 2012; Trout, Brettmann, & Myerson, 2013). The first significant patent in this topic presents a rotating charged cylindrical electrode immersed into the solution as the starting surface of fiber generation (Jirsak et al., 2003). This technology has been commercialized by Elmarco as *Nanospider*™ (Figure 3a; Elmarco s.r.o, n.d.). Subsequently, the cylinder was changed to a wire in the second generation of Nanospider™ technology in 2010. The main alteration in this technology compared to the cylindrical method is that the spinneret does not move and instead of immersion, the solution covers the stationary wire by using a continuous feeding system. Alongside the Nanospider™ technologies, many other free surface ES techniques have been published to increase the productivity using different types of spinnerets such as *beaded-chain*, *spiral coil*, *balls*, *bubbles*, and so on (Liu et al., 2008, 2014; Miloh et al., 2009; Smit & Sanderson, 2009a, 2009b; Wang et al., 2012). Free surface ES methods also have some disadvantages, which complicate the practical application, especially in the pharmaceutical field. Probably the most

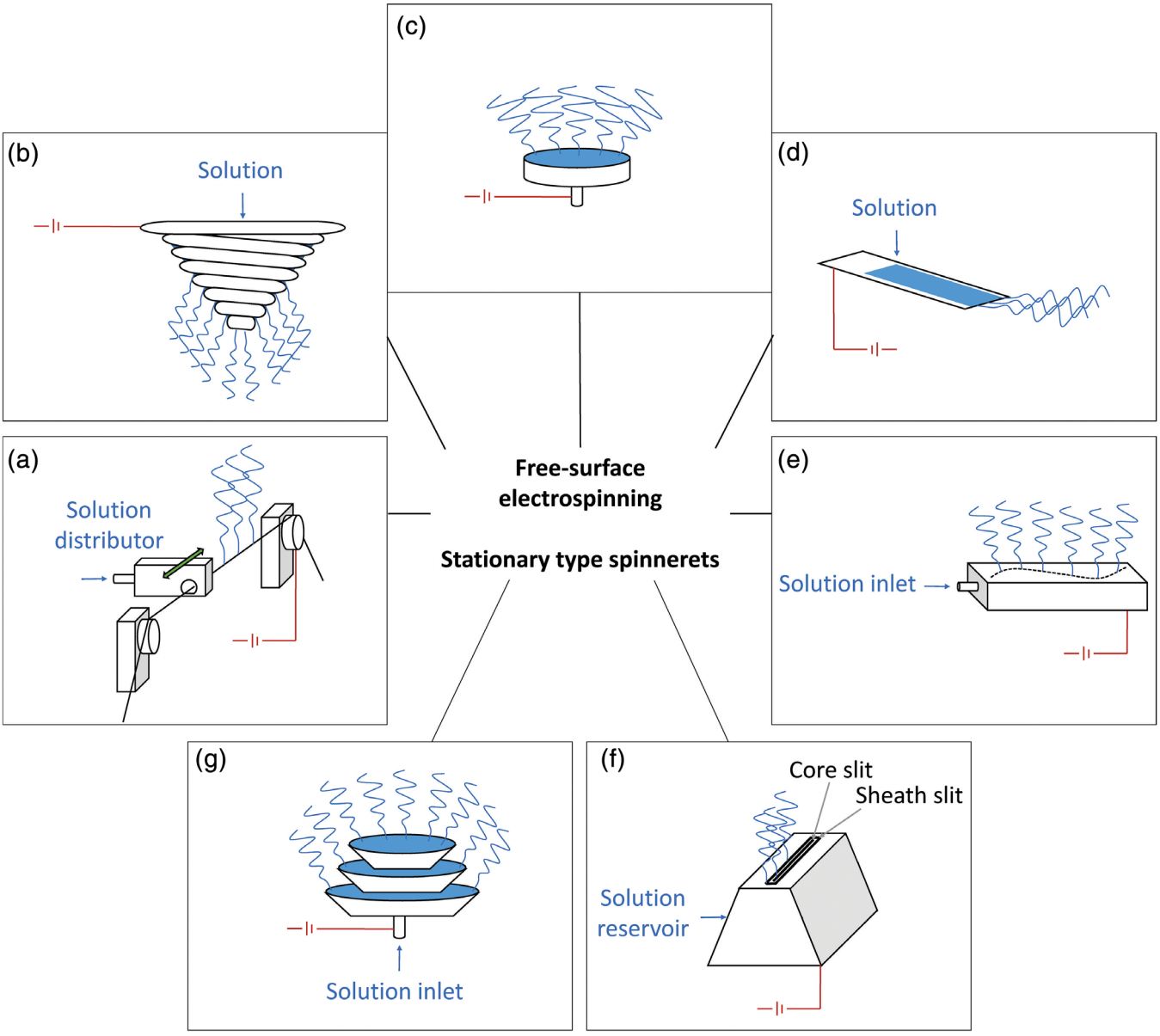

FIGURE 3 Stationary free surface electrospinning methods, (a) wire; (b) conical wire; (c) bowl; (d) plate edge; (e) curved slot; (f) slit; (g) stepped pyramid

important one is the fast evaporation of volatile solvents, in which poorly water-soluble drug compounds can typically be dissolved. This phenomenon results in a continuously changing concentration in the liquid film, which makes the process difficult to control.

In 2012, *corona ES* (Figure 4i) was developed to minimize the free liquid surface and maximize the jet formation using a rotating ring as a spinneret (Molnar & Nagy, 2016; Molnár, Nagy, Marosi, & Mészáros, 2012).

By the combination of corona ES and high-speed rotation, *free surface high-speed ES* (Figure 4j) was developed. About 450 g/hr productivity was reached using this technology, which might fulfill the capacity requirements of the pharmaceutical industry (Nagy et al., 2015). However, the presence of free liquid surface (even though minimized) can cause some technical difficulties in the case of extremely volatile solvents (e.g., dichloromethane) or extremely concentrated solutions (e.g., polymer-free cyclodextrin-based solution). To avoid these problems, the free liquid surface was eliminated by developing a spinneret equipped with multiple orifices. This enables the production of large quantities of fibers while the concentration of the solution remains constant (Vass, Démuth, Farkas, et al., 2019).

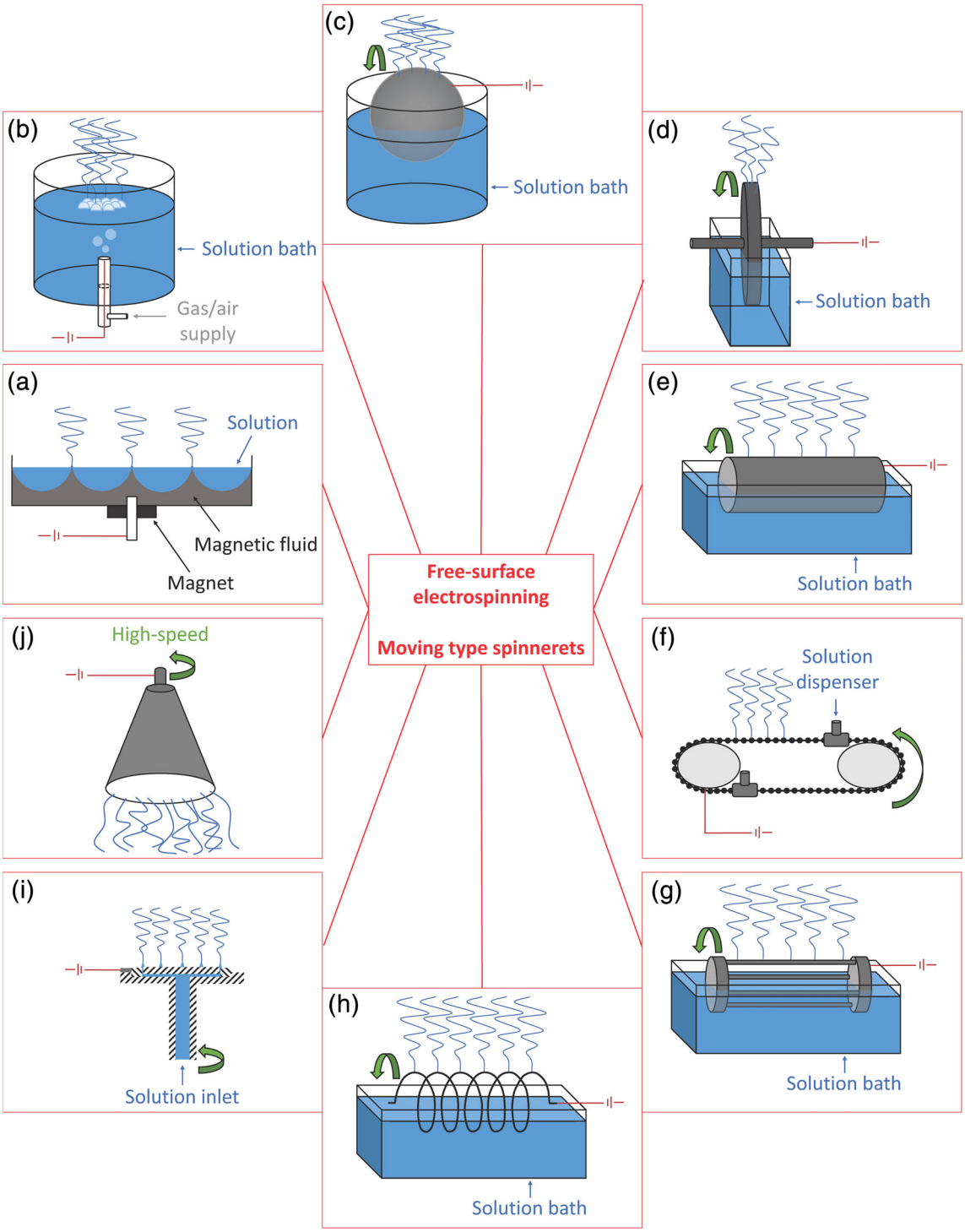

FIGURE 4 Moving free surface electrospinning methods, (a) magnetic fluid; (b) bubble; (c) ball; (d) rotary disk; (e) cylinder; (f) beaded-chain; (g) rotary wire; (h) spiral coil; (i) corona; (j) free surface high-speed

3 | APPLICATIONS OF SCALED-UP ES IN THE PHARMACEUTICAL INDUSTRY

During the past decade, the number of publications dealing with electrospun drug delivery systems increased exponentially. Laboratory-scaled ES has been used for antibiotics (Zupančič et al., 2018), wound dressings (Tamm et al., 2016), antifungal (Veras, Roggia, Pranke, Pereira, & Brandelli, 2016), anti-allergic (Abdelhakim, Coupe, Tuleu, Edirisinghe, & Craig, 2019), anti-inflammatory (Sipos, Kósa, Kazsoki, Szabó, & Zelkó, 2019), and anticancer drugs (Liu et al., 2013; Ma et al., 2011), and

so on. The reader is directed to excellent and detailed reviews for further information on this topic (Chen, Li, Li, & Xie, 2018; Ding et al., 2019; Hu et al., 2014; Kajdič, Planinšek, Gašperlin, & Kocbek, 2019; Qi & Craig, 2016; Sebe, Szabó, Kállai-Szabó, & Zelkó, 2015; Seeram, Zamani, & Molamma, 2013; Sill & von Recum, 2008; Topuz & Uyar, 2018).

Even though numerous scaled-up ES technologies have been developed (see Section 2), there are only a handful of articles discussing the utilization of scaled-up ES for the formulation of oral drug delivery systems. This section aims to cover these works and compare the productivity increase that can be achieved by the different techniques. Table 3 summarizes the different active compounds produced by scaled-up ES technologies.

3.1 | Nozzle-type technologies

In the context of pharmaceutical applications, only a few nozzle-based technologies have been investigated for scaled-up production so far. The Fluidnatek LE-100 and LE-500 manufactured by Bioinicia are GMP-certified scaled-up ES/electrospraying machines which can be used for pharmaceutical applications (Bioinicia, n.d.). The Fluidnatek machines employ *multiple needles* to increase process productivity. *Electroblowing* is one of the stationary nozzle methods which seemed to be appropriate to satisfy the pharmaceutical needs. Um et al. compared ES and electroblowing using a hyaluronic acid-containing system (Um et al., 2004). Their results highlight the advantages of the applied air blow such as the faster solvent evaporation and the higher feeding rate. Publication of Balogh et al. confirmed the latter statement since five times higher flow rate was achieved with electroblowing compared to SNES (Balogh, Horváthová, et al., 2015). In this work, the air-assisted method was successfully applied for preparing fibrous diclofenac sodium-cyclodextrin complex-based reconstitution injection. Even higher feeding rate was reached with electroblowing in the case of itraconazole-loaded samples (Sóti et al., 2015). In this work, the authors compared electroblowing to spray drying and they not only showed that increased productivity (50 g/hr) is achievable using the air-assisted technology, but they also demonstrated that the prepared amorphous solid dispersion showed better stability than the spray-dried samples.

For pharmaceutical applications, technologies applying *rotary spinnerets with multiple holes* proved to be the most researched techniques. Sebe et al. published several articles about high-speed rotary spinning, a technique with 60 g/hr productivity (Sebe et al., 2013). The centrifugal forces facilitated a faster and more cost-effective production of microfibers possessing appropriate properties to be used in B_{12} tablets (Sebe, Bodai, et al., 2015). Application of spinneret with orifices and pressure (pressurized gyration) without voltage led to the increased production rate of ibuprofen-PVP K90 fibers which could satisfy the needs of the pharmaceutical industry (Raimi-Abraham, Mahalingam, Davies, Edirisinghe, & Craig, 2015). Nozzle-based high-speed ES was successfully applied to prepare a reconstitution injection dosage form of voriconazole-loaded fibers with 240 g/hr productivity. The reconstitution tests showed similarity to the commercially available formulation prepared by freeze drying (Vass, Démuth, Farkas, et al., 2019).

3.2 | Free surface ES

Brettmann et al. prepared albendazole and famotidine containing fibers with a throughput of 1.2 g/hr by using a *rotating wire spindle* in an attempt to increase the dissolution rate of active pharmaceutical ingredients (APIs; Brettmann, Cheng, Myerson, & Trout, 2013). Radácsi et al. used a *rotating copper wire coil* partially submerged in the ES solution to produce niflumic acid-containing fibers with improved dissolution kinetics. This setup enabled the production of 100 mg material in 10 min (Radacsi et al., 2019). El-Newehy et al. prepared polyvinyl alcohol, polyethylene oxide and metronidazole containing nanofibers by the *Nanospider*™ technology for creating a controlled-release system (El-Newehy, Al-Deyab, Kenawy, & Abdel-Megeed, 2012). The API release of the fibers reached 84% within 2 hr and the fibrous samples showed remarkable antimicrobial activity against the investigated pathogens. Krogstad and Woodrow compared a single-needle apparatus and a Nanospider™ equipment. The tenofovir-loaded polyvinyl alcohol fibers produced by the two technologies were found to have similar morphology and release profile and this proved the wire technique to be a possible way for scaled-up production of drug-loaded fibers in the case of nonvolatile aqueous solutions. The productivity of the Nanospider technology was 7.6 g/hr when using a single wire of 25 cm length (Krogstad & Woodrow, 2014). *Free surface high-speed ES* has been used to prepare itraconazole-loaded fibers with 450 g/hr productivity (Nagy et al., 2015). The morphology and the dissolution properties of the produced fibrous mats showed similarity to the samples prepared by SNES. It has been shown that rational selection of the applied polymer can ensure the

TABLE 3 Summary of active compounds produced by scaled-up electrospinning technologies

Active compound	Therapeutic effect	Fiber matrix	Final dosage form	Technology	Productivity	Reference
$AgNO_3$, Chitosan	Antibacterial	Chitosan, PVA, $AgNO_3$, TiO_2	Nanofiber mats	Needleless electrospinning	~50 g/hr	Wang, Zhang, Gao, and Pan (2016)
Carvedilol	Beta blocker	Eudragit E	Melt electrospun fibers	Melt electrospinning	~0.65 g/hr	Nagy et al. (2013)
Carvedilol	Beta blocker	Eudragit E, Eudragit L 100-55, PVPK90	Drug-loaded fibers	Alternating current electrospinning	~11.5 g/hr	Balogh et al. (2015)
Dexamethasone	Anti-inflammatory	PLGA, PCL	Core-sheath micro- and nanofibers	Slit-surface electrospinning	~50–250 g/hr	Yan et al. (2015)
Diclofenac sodium	Nonsteroidal anti-inflammatory	HP-β-CD	Reconstitution injection	Electroblowing	~7.76 g/hr	Balogh, Horváthová, et al. (2015)
Hyaluronic acid	Wound healing	Hyaluronic acid	Nonwoven nanofiber membrane	Electroblowing	~0.06 g/hr	Um, Fang, Hsiao, Okamoto, and Chu (2004)
Iodine	Antimicrobial	PVPK25, PVPVA64	Fiber tissue	High-speed rotary spinning	~60 g/hr	Sebe et al. (2013)
Itraconazole	Antifungal	Eudragit E	Nonwoven nanofibrous mat	Electroblowing	~56.7 g/hr	Sóti et al. (2015)
Itraconazole	Antifungal	PVPVA64	Polymer nanofibers	Free surface high-speed electrospinning	~450 g/hr	Nagy et al. (2015)
Itraconazole	Antifungal	PVPVA64	Tablet	Free surface high-speed electrospinning	~350 g/hr	Démuth et al. (2017), Démuth, Farkas, Balogh, et al. (2016)
Melatonin	Insomnia treatment	Cellulose acetate, PVP	Mono- and three-layered tablets	Co-electrospinning	~10 mg/hr	Vlachou et al. (2019)
Niflumic acid	Anti-inflammatory/analgesic	PVP	Capsule	Nozzle-free electrospinning	~0.6 g/hr	Radacsi, Giapis, Ovari, Szabó-Révész, and Ambrus (2019)
Semisynthetic alkaloid derivate	–	Hydroxypropyl cellulose, citric acid monohydrate	Microfiber-based tablets	High-speed rotary spinning	–	Szabó, Kállai-Szabó, Sebe, and Zelkó (2014)
Spironolactone	Antihypertensive	Eudragit FS 100	Fibrous fabrics	Alternating current electrospinning	~2.81 g/hr	Balogh et al. (2017)
Spironolactone	Antihypertensive	HPMC 2910-PEO	Electrospun plume	Alternating current electrospinning	~6.5 g/hr	Balogh et al. (2016
Spironolactone	Antihypertensive		Electrospun fibers		~3 g/hr	Balogh et al. (2017)

(Continues)

TABLE 3 (Continued)

Active compound	Therapeutic effect	Fiber matrix	Final dosage form	Technology	Productivity	Reference
		HPMCAS, SDS/NH_4Ac/$CaCl_2$		Alternating current electrospinning		
Spironolactone	Antihypertensive	PVPK90, SDS	Nanofibrous plume	Corona-alternating current electrospinning	~117 g/hr	Farkas et al. (2019)
Spironolactone	Antihypertensive	PVPVA64, PVPK30, HPMC	Tablet	Free surface high-speed electrospinning	~70 g/hr	Szabó et al. (2018)
Tenofovir	Microbicide/nucleotide reverse transcriptase inhibitor	PVA	Fiber mesh	Free surface electrospinning (Nanospider™)	~7.6 g/hr	Krogstad and Woodrow (2014)
Vitamin B_{12}	Red blood cell formation, and so on	PVPK30	Tablet	High-speed rotary spinning	~60 g/hr	Sebe et al. (2015)
Voriconazole	Antifungal	SBE-β-CD	Reconstitution powder for infusion	Nozzle-based high-speed electrospinning	~240 g/hr	Vass, Démuth, Farkas, et al. (2019)
β-galactosidase	Lactose intolerance treatment	PVA, PEO, Mannitol	Tablet	Nozzle-based high-speed electrospinning	~9.2 g/hr	Vass et al. (2019)
β-galactosidase	Lactose intolerance treatment	HP-β-CD	Tablet	Nozzle-based high-speed electrospinning	~270 g/hr	Vass et al. (2020)

stability of the amorphous drug in the matrix which meets the strict requirements of the pharmaceutical industry (Démuth et al., 2016). The technology proved to be appropriate for the formation of flubendazole containing electrospun product as well (Vigh et al., 2017). Both the drug-loaded nanofibers and the tablets filled with the fibers had outstanding dissolution properties. Moreover, in vivo tests proved that the bioavailability of the amorphous drug form found in the fibers was much higher than the crystalline API's.

3.3 | Other scaled-up ES approaches for drug delivery

3.3.1 | Melt ES

Solvent-free fiber-forming methods are feasible ways for preparing amorphous solid dispersions besides solvent-based techniques. Melt ES (MES) is a solvent-free solution for the continuous production of area fibrous mats with high surface area (Dalton, Joergensen, Groll, & Moeller, 2008; Dalton, Klinkhammer, Salber, Klee, & Möller, 2006; Dalton, Lleixà Calvet, Mourran, Klee, & Möller, 2006; Deng et al., 2009; Hutmacher & Dalton, 2011; Nagy et al., 2013). By preparing amorphous solid dispersions this way, there is no need to use expensive solvent recovery and the risk of solvent explosion can be avoided. Additionally, there will be no residual solvent content in the fibers, which needs to be strictly controlled when using solvent-based methods. When MES is coupled with melt extrusion, it can be operated with high productivity to prepare large surface area amorphous solid dispersions. Nagy et al. formulated the composition of Eudragit® E and 20% carvedilol into amorphous solid dispersions in order to enhance the dissolution of carvedilol in acidic media such as gastric acid (Nagy et al., 2013). The average diameter of the fibers prepared with MES was one order of magnitude larger than that of the solvent-based ES fibers. However, the drug release was completed in 2 min in the case of both formulations representing immediate drug release. Beside its advantages, MES has a few limitations, like the thermal degradation of sensitive compounds when high process temperature is applied during melt extrusion. Balogh et al. could avoid this phenomenon by using plasticizers during the process (Balogh et al., 2014). Without these additives, 155°C was required for the processing of an Eudragit® E-carvedilol composition with MES. Introducing triacetin, tween 80, and polyethylene glycol 1500 as plasticizers, the process temperature could be reduced by 20–135°C. This significantly lowered the amount of impurities according to the HPLC measurements after 1 month of storage, and the fast release of the drug could still be maintained. The productivity of MES can be further increased with multi-needle spinning heads or needleless ES (Fang, Zhang, Sutton, Wang, & Lin, 2012).

3.3.2 | Alternating current ES

Most of the research articles about electrospinning report the use of direct current power supply, however, several advantages may be gained when replacing it with an alternating current power source (Kessick, Fenn, & Tepper, 2004; Lawson, Stanishevsky, Sivan, Pokorny, & Lukáš, 2016; Maheshwari & Chang, 2009; Sarkar, Deevi, & Tepper, 2007). Pokorny et al. produced polyacrylonitrile and fibrous mats with alternating current ES (ACES; Pokorny et al., 2014). They pointed out that during ACES multiple jets are formed on the surface of the liquid droplet leaving the alternately charged spinneret, while only one jet is formed during DCES, which is shown in Figure 5. This could be one of the main reasons for the increased productivity of ACES. An important feature of ACES is that it is a collectorless method, which creates a plume of fibers. It was suggested that the movement of the fibrous plume is mainly affected by the electric wind surrounding the spinneret (Balogh et al., 2016). Frequency and waveform of the high voltage appear as new process factors when using ACES, and their optimization can also result in increased productivity. ACES is capable of producing yarns as well, which are the building blocks of tissue engineering and composite-based products (Sun et al., 2014).

The first pharmaceutical application of ACES was reported by Balogh et al. for the production of amorphous solid dispersions. They achieved the controlled release of carvedilol using different pharmaceutically relevant polymers such as Eudragit® E, Eudragit® L 100–55 and polyvinylpyrrolidone K90 (Balogh, Cselko, et al., 2015). Using ACES they managed to prepare amorphous drug-loaded fibrous mats of excellent quality with increased feeding rates (from 10 to 40 ml/hr) compared to single-needle DCES (5 ml/hr). The prepared fibers showed enhanced drug release at gastric, neutral, and colonic pH. ACES has also been successfully applied for processing Eudragit® FS, a novel methacrylate

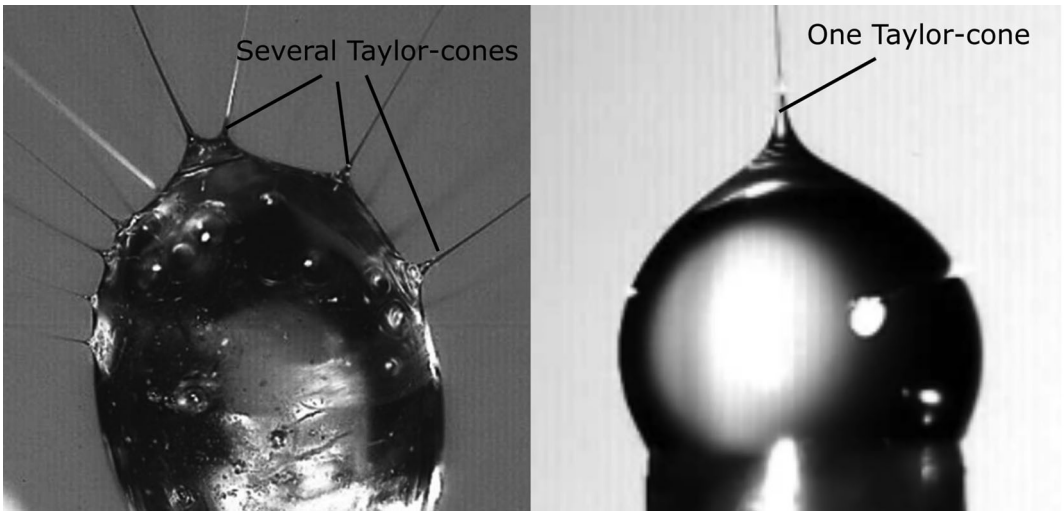

FIGURE 5 Comparison of Taylor-cone formation using direct current electrospinning and alternating current electrospinning (Pokorny et al., 2014)

terpolymer dissolving only in the colon (Balogh, Farkas, Domokos, et al., 2017). The authors prepared nanofibrous amorphous solid dispersions for the targeted release of spironolactone.

Cellulose-based polymers are one of the most important carriers in the preparation of marketed amorphous solid dispersions (Jermain, Brough, & Williams 3rd., 2018). Balogh et al. investigated the AC spinnability of cellulose-based carriers for controlled drug delivery (Balogh et al., 2016). In the case of HPMC 2910, the insufficient spinnability with both ACES and DCES was overcome by introducing different grades of polyethylene oxides (100 kDa, 1 MDa, and 4 MDa) to the polymer solutions. These polymers are excellent fiber-forming agents even at low concentrations (0.03–4%). This way good quality amorphous drug-loaded fibers could be electrospun, which showed an increased release of the model drug spironolactone. As next step, the formulation of a similar cellulose derivative, HPMC acetate succinate was attempted with ACES. However, only fibers with poor quality could be prepared even after the addition of polyethylene oxide to the solutions (Balogh, Farkas, Palvolgyi, et al., 2017). The investigation of the effect of solution properties (surface tension, viscosity, and conductivity) on fiber formation showed that ACES is highly sensitive to changes in solution conductivity and therefore it needs to be thoroughly optimized. After setting the optimal conductivity using different salts (sodium dodecyl sulfate, calcium chloride, and ammonium acetate), fibers of excellent quality could be electrospun by ACES with increased productivity. Due to the amorphous drug content and large surface area, the prepared formulations showed enhanced drug release at pH = 6.8.

Several attempts have been made to improve the productivity of DCES by modifying the applied spinneret. One of the most effective solutions is corona ES, where the conventional needle-like nozzle is replaced with a corona electrode (Figure 4). Further improvements were carried out by Farkas et al. resulting in the development of corona alternating current ES (C-ACES). In the case of this technique the same corona spinneret is applied but with an AC power source for fiber formation. This way a two order of magnitude increase (1,200 ml/hr maximum) could be achieved in productivity compared to the single-needle DCES method (Farkas et al., 2019). C-ACES proved to be feasible for the production of amorphous solid dispersions for enhanced drug release, maintaining the advantageous properties achievable by the DCES process. The productivity of C-ACES comes close to the most productive ES method, high-speed ES, showing that ACES is also a promising solution when the productivity increase of ES is required.

3.4 | Production of nanofibers with complex structures

Electrospun monolithic ASDs were first developed for the purpose of achieving the immediate release of poorly soluble APIs (Ignatious & Baldoni, 2001). However, after a vast amount of knowledge was accumulated about the ES process, researchers started to modify this technology in order to produce sustained release formulations (Chou, Carson, & Woodrow, 2015; Kenawy et al., 2002; Verreck et al., 2003; Yu et al., 2018). This was done by producing monolithic ASDs with a hydrophobic polymer matrix (Puppi & Chiellini, 2018; Ranjbar-Mohammadi, Zamani, Prabhakaran, Bahrami, &

Ramakrishna, 2016; Xu, Zhong, Zhou, Trajtman, & Alfa, 2010) and by inventing new ES methods that yield nanofibers consisting of complex nanostructures (Yu et al., 2018). The latter includes core/shell structures (He et al., 2018), trilayered fibers (Jouybari et al., 2019; Liu et al., 2019), hollow fibers (Huang, Wu, Wong, Qu, & Srivatsan, 2018), and Janus fibers (Yao et al., 2019; side-by-side configuration). These technologies are based on special spinnerets, which enable the simultaneous processing of two or more liquid streams. They can be separated into two main classes: coaxial/triaxial ES and side-by-side ES. In the case of coaxial ES, the applied spinneret consists of two needles which are coaxially placed together. The core of the produced fiber is formed from the solution injected in the internal needle, while the shell comes from the outer needle (Buzgo, Mickova, Rampichova, & Doupnik, 2018). Similarly, triaxial ES uses three coaxial needles to produce three-layered nanofibers. However, due to the complexity of this process only limited results are available (Khalf & Madihally, 2017). Hollow nanofibers can be obtained by using heat treatment or a specific solvent to remove the core during coaxial ES (Huang, Wu, et al., 2018). Janus fibers can be produced by placing two needles side-by-side (Chen et al., 2015). Figure 6 shows the structure and the product of these technologies. A general advantage of multilayer ASDs over their monolithic counterparts is that their structure can be engineered for their specific purpose. For example, monolithic ASDs designed for sustained release always suffer from an initial burst dissolution phenomenon, since due to the homogeneous distribution of the API in the matrix, some API molecules will be directly on the surface of the fiber (Sharma et al., 2014). Coaxial ASDs can easily circumvent this problem by using a blank polymer as shell and placing the API in the core of the fiber (Yu et al., 2013). Since the first publication of the technology (Sun, Zussman, Yarin, Wendorff, & Greiner, 2003), coaxial electrospun core/shell nanofibers have been utilized for a variety of purposes including tissue engineering (Sperling, Reis, Pranke, & Wendorff, 2016; Wang et al., 2019), sensor technology (Huang et al., 2018), and production of lithium ion batteries (Zhang et al., 2019).

Multilayer ASDs can be tailored to enable a biphasic dissolution of the drug so that an initial fast dissolution phase ensures a quick effect, and this is followed by a sustained release phase which maintains the effect. Yu et al. produced core/shell nanofibers containing ketoprofen using polyvinylpyrrolidone as shell and ethyl cellulose as core polymer (Yu et al., 2013). It was observed that by adjusting the flow rate of the shell solution, the amount of immediately released API could be controlled. Complex nanofiber structures are also able to release two or more APIs simultaneously in a controlled way. Jouybari et al. used triaxial ES to produce nanofibers containing three anticancer drugs (Jouybari et al., 2019). The performance of the triaxial system was examined and all three drugs were released in a controlled way. Multilayer systems are capable of pH-sensitive drug release. Yang et al. developed a colon-targeted release formulation which does not release the drug under acidic conditions (Yang et al., 2016). Core/shell structures are a promising tool for enhancing the stability of the amorphous API. With an appropriate shell polymer, the amorphous drug encapsulated in the core can be protected from humidity, light, heat, and oxygen (Yu et al., 2018). For more information on the utilization of multilayer ASDs in the pharmaceutical field, the reader is directed to the following review articles (Aytac & Uyar, 2018; Khalf & Madihally, 2017; Lu et al., 2016; Senthamizhan, Balusamy, & Uyar, 2017; Tyo et al., 2019; Yu et al., 2018).

The aforementioned results clearly demonstrate the potential of multilayer ASDs. However, in order to capitalize on their advantages, their production on an industrial scale needs to be accomplished. So far only a few articles have discussed the scale-up of coaxial ES. Duan and Greiner (2019) used air-blowing-assisted coaxial ES to produce core/shell, metal-in-carbon, and hollow fibers. They reported total flow rates between 5.8 and 12 ml/hr, which is an almost 10-fold increase compared to regular coaxial ES. Jiang et al. proposed a free surface ES method using a stepped pyramid-shaped

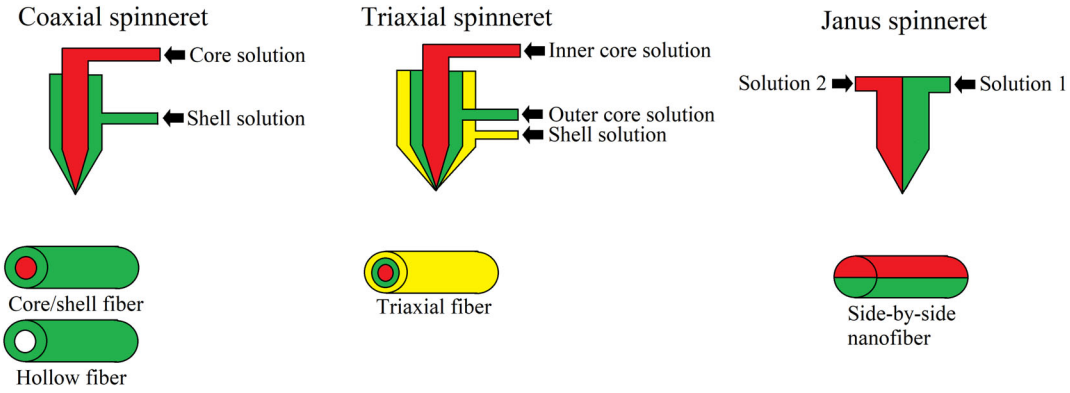

FIGURE 6 Needle setup and product of coaxial, triaxial, and Janus ES. ES, electrospinning

spinneret (Jiang & Qin, 2014). This method allowed the simultaneous formation of multiple coaxial jets while also preventing clogging. Vysloužilová et al. realized needleless ES using a weir spinneret (Vysloužilová et al., 2017; Vysloužilová, Valtera, Pejchar, Beran, & Lukáš, 2014). Yan et al. developed the slit-surface ES technology (Yan et al., 2015). Their apparatus consists of two triangular-shaped nozzles aligned along a single vertical plane (Pham et al., 2013; Sharma, Pham, et al., 2014; Sharma, Pham, & Marini, 2015). This enables the physical co-localization of two liquids along one dimension. The technology was applied to produce various types of complex nanofibers with feeding rates reportedly exceeding 1 L/hr. Several companies (e.g., InoCure) have developed their own solutions of high throughput ES (InoCure s.r.o, n.d.; Persano, Camposeo, Tekmen, & Pisignano, 2013), and some of these instruments can also be used with a coaxial spinneret. Considering some of the existing scale-up technologies of single fluid ES described in the previous chapters of this article, it is likely that in the near future more solutions will appear that aim to enhance the productivity of multiple-fluid ES.

3.5 | Biopharmaceutical application of scaled-up ES

Nowadays, the demand for biopharmaceutical products is growing rapidly. However, the manufacturing of these therapeutics is challenging. Owing to their complex structure, exposure to environmental stress can cause degradation during production, shipping and storage, especially in liquid dosage forms (Angkawinitwong, Sharma, Khaw, Brocchini, & Williams, 2015). The solid formulation is often required to retain the stability of biopharmaceuticals. Freeze drying and spray drying are the most widely used technologies to dehydrate biopharmaceuticals, but in some cases they do not provide sufficiently gentle drying, which can result in the loss of biopharmaceutical activity (Emami, Vatanara, Park, & Na, 2018; Vass et al., 2019). ES provides rapid solvent evaporation at ambient conditions (room temperature and atmospheric pressure), which makes it a gentle drying technology that might be used as an alternative to freeze drying and spray drying. The technology has been used for the solid formulation of various biopharmaceuticals, including nucleic acids, peptides, proteins (enzymes, hormones, monoclonal antibody, etc.), bacteria, vaccines, and so on (Angkawinitwong, Awwad, Khaw, Brocchini, & Williams, 2017; Choi, Han, Hyun, & Yoo, 2016; Knockenhauer, Sawicka, Roemer, & Simon, 2008; Lancina, Shankar, & Yang, 2017; Škrlec et al., 2019; Wagner et al., 2015; Zeng et al., 2005).

In the case of sensitive large molecules or probiotics, the use of water instead of organic solvents is required to maintain the active form. Owing to the relatively high boiling point of aqueous solutions, the evaporation of the solvent requires more time. Thus, the productivity of the aqueous SNES process is reduced (0.02–0.5 g/hr) compared to the volatile organic solvents. There have been attempts to increase the productivity by the scale-up of the ES process using water-based solutions. Needleless ES of polyvinyl alcohol-chitosan aqueous solution with a spinning cylinder spinneret was applied and 50 g/hr productivity was achieved (Wang et al., 2016). The fibers were collected on a rotating drum, however, during continuous operation evaporation of water from the free liquid surface can be notable (Sousa et al., 2015). Besides needleless ES, nozzle-based high-speed ES was applied for the drying of aqueous polyvinyl alcohol solutions with high productivity (Hirsch et al., 2019). Using a pilot-scale high-speed ES equipment connected to a cyclone, an aqueous hydroxypropyl-beta-cyclodextrin solution was electrospun and a 240 g/hr production rate was achieved by Vass, Démuth, Farkas, et al. (2019). Furthermore, Vass et al. were successful in ES nanofibers incorporating β-galactosidase, an enzyme used for the treatment of lactose intolerance, in a polyvinyl alcohol-based as well as in a cyclodextrin-based matrix and from both systems they obtained grindable fibers. This made the production of tablets as an oral dosage form possible (Vass et al., 2020; Vass, Hirsch, Kóczián, et al., 2019). These examples show that nozzle-based high-speed ES is suitable for the scale-up of ES and can be used for the solid formulation of both small and large molecules.

4 | DOWNSTREAM PROCESSING OF THE ELECTROSPUN FIBERS

The majority of the publications related to fiber spinning are focusing on how to manufacture fibers with appropriate characteristics, such as the desired diameter (small or large) or drug release (immediate or controlled). A smaller group is dealing with the scale-up of the different technologies as it is shown in this review. However, only a few articles present ways to convert the obtained fibers into applicable pharmaceutical formulations in spite of the opportunity that was opened up for such investigations by the scaled-up production of drug-loaded fibers. This chapter is dedicated to

showing the downstream processing options for transforming the obtained fibers, which generally means tablet formation.

4.1 | Non-conventional tablet/capsule formation

As producing oral dosage forms from nanofibrous mats in the traditional way (milling, homogenization with excipients, tableting) does not seem evident, several research groups attempted to use nonconventional methods to obtain this type of products. In these cases, the nonwoven sheet is not milled and not homogenized with tableting excipients before compression. Researchers from MIT patented two solutions of theirs to form tablets with electrospun materials. The main invention of the first study is that the fibrous sheet is first folded/rolled up, and then this product can be cut or coated to make tablets (Trout et al., 2015). According to the second patent, electrospun fibers can be deposited on an elongated rod that is subsequently moved to a die (Slocum, Sondej, Trout, Rutledge, & Bhattacharyya, 2016). In the cavity, the fibrous mat is stripped off the rod, compressed and then ejected. Hamori et al. prepared tablets by compressing nanofibers containing methacrylic acid copolymer S (Eudragit® S100; Hamori et al., 2015, 2016). As expected and desired, controlled-release systems could be obtained as tablets did not disintegrate in the upper intestine lumen. Monolayered and three-layered tablets for the controlled release of melatonin have also been prepared from electrospun fibers (Vlachou et al., 2019). In the case of the three-layered tablet, the upper and lower layer consisted of lactose and HPMC to control the drug release from the middle layer. Similarly (without excipients), nanofibers containing PVP and prednisone were compressed into minitablets (Poller, Strachan, Broadbent, & Walker, 2017). Prednisone is a poorly soluble drug, and therefore the dissolution enhancement of the API was also aimed by the authors. Immediate release of the incorporated drug was accomplished, presumably owing to the small size of the tablets. Radacsi et al. prepared fibers containing niflumic acid with improved dissolution rate and bioavailability. The fibers were mixed with a filler agent in a Turbula mixer, which was followed by capsule filling of the prepared mixtures (Radacsi et al., 2019). However, mass production via these aforementioned methods seems questionable as they do not fit into the current tablet manufacturing processes.

4.2 | Conventional tablet formation

4.2.1 | Collection of the fibers for milling

The conventional way of producing tablets from the electrospun material starts with the collection of the fibers, followed by milling, homogenization with excipients and finally the compression into tablets. The first step is always the continuous collection of the nonwoven sheet. On industrial-scale ES machines, which are nowadays mainly applied for non-pharmaceutical purposes, such as NanoSpinner™ 416 or Nanospider™ NS 8S1600U, a substrate web potentially made of cellulose, synthetics, fiberglass, or foils with a width of 1–1.7 m is used for capturing the fibers. Similarly, Szabó et al. developed a continuous collector equipped with PP collecting fleece and a doctor blade that removes the fibers (Figure 7; Szabó et al., 2018).

A similar type of collection, which is not yet suitable for scaled-up ES, was developed by Balogh and co-workers in two recent publications (Balogh et al., 2018; Domokos et al., 2019). The drug-loaded fibers are electrostatically deposited onto a pullulan film attached to a moving roll. This technology is not designed to produce tablets (however, it seems possible with minor modifications): the obtained sheet was cut into immediate release orally dissolving webs.

A very effective collection after high-speed ES can be performed by a cyclone, similarly to spray drying (Figure 8; Vass, Démuth, Farkas, et al., 2019; Vass et al., 2020). The fast circular motion of the fibers in the cyclone results in their fragmentation. This can be advantageous if the fibers are to be processed into tablets, as the next step of the formulation is grinding.

4.2.2 | Grinding of the fibers

Grinding of the fibers could be a crucial step in the formulation, however, not much information can be found about this subject in the literature. Presumably, the grindability of the electrospun sheets mainly depends on the type and the molecular weight of the applied polymer (the higher the molecular weight, the poorer the grindability), besides other

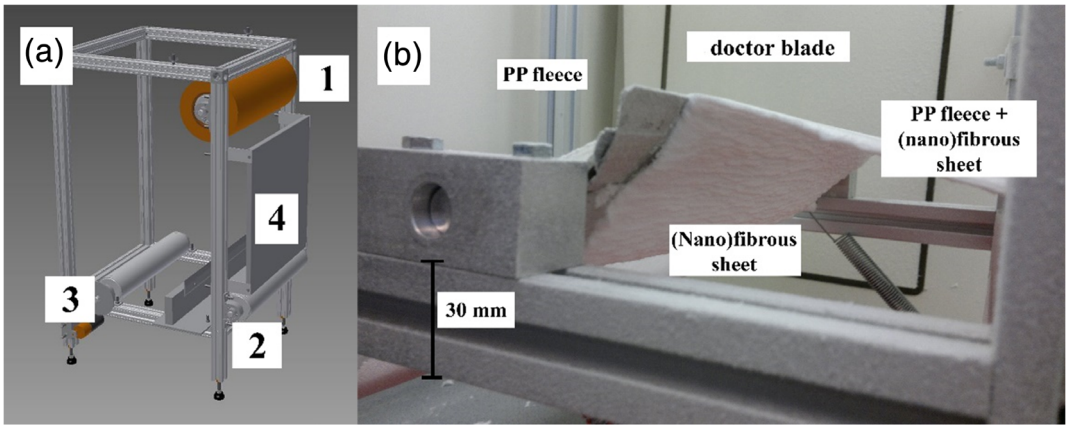

FIGURE 7 Equipment for collecting fibers: (a) a 3D image showing the whole equipment, (b) an image showing the equipment during the collection of PVPVA64 fibers with the doctor blade removing it (Szabó et al., 2018)

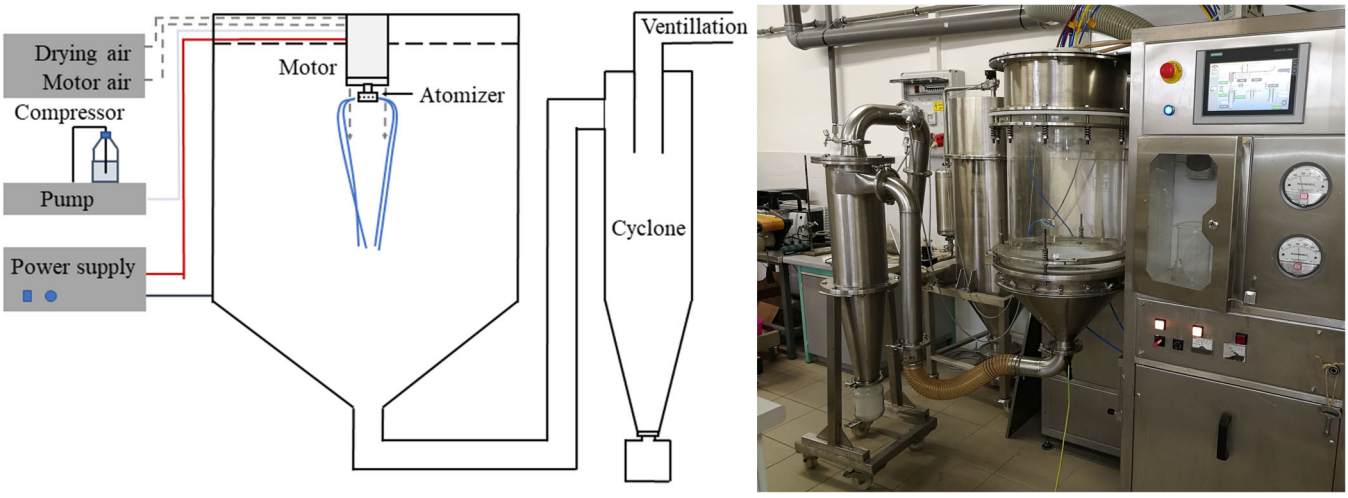

FIGURE 8 Schematic drawing and photo of a nozzle-based high-speed ES machine equipped with cyclone collecting the produced fibers (Vass et al., 2020). ES, electrospinning

factors like fiber diameter, residual moisture, and the plasticizer effect of the API. Microfibers obtained by high-speed rotary spinning technique (without voltage) have been ground via two methods. In the first case, a vibrating mill was applied for the micronization of the fibers after the first fine cutting (Sebe, Bodai, et al., 2015). In the other study, the mat was ground by means of a grinder equipped with knives (Szabó, Kállai-Szabó, Sebe, & Zelkó, 2014). SEM images proved the fragmented state of the fibers. Grinding of nanofibers prepared by high-speed ES has been performed by a hammer mill, a cutting mill, and an oscillating sieve mill (Démuth et al., 2017;Hirsch et al., 2019; Vass, Hirsch, Kóczián, et al., 2019). All the tested techniques could be successfully applied for the purpose. Grindability of fibers made of polyvinyl alcohol and polyethylene oxide could be enhanced by the addition of sugars or sugar derivatives such as glucose or mannitol to the ES solution (Hirsch et al., 2019; Vass, Hirsch, Kóczián, et al., 2019). Based on these results, it seems that milling of the nonwoven sheets can be performed on conventional equipment and it can be a crucial technology to obtain a powder ready for homogenization and tableting.

4.2.3 | Tableting of the ground fibers

A few examples can be found in the literature where fibrous mats are processed into conventional tablets via a traditional process (milling followed by homogenization with excipients and compression; Démuth et al., 2016; Démuth

et al., 2017; Sebe, Bodai, et al., 2015; Szabó, Kállai-Szabó, Sebe, & Zelkó, 2014). Generally, the properties of the prepared blends (particle size distribution, flowability) and tablets (hardness, friability, disintegration time, dissolution) are examined and published. However, the systematic exploration of the tableting process is usually not in the focus of the studies. When electrospun nanofibers containing PVPVA64 and itraconazole were investigated in terms of compression behavior (Démuth et al., 2017), it was shown that the fibrous material can take up a large percentage of tablet volume due to its low bulk density. As the ground fibers form a gelling network, disintegration is hindered when the amount of excipients (especially fillers) is small. In spite of the low bulk density and the relatively poor flowability, rotary tableting could be carried out and tablets with acceptable weight variation could be obtained (Démuth, Farkas, Balogh, et al., 2016). To process a nonwoven sheet to tablets in a continuous manner also seems feasible, which could potentially be a really important feature in the future (Szabó et al., 2018). To summarize, the conversion of fibrous sheets into conventional tablets seems possible; however, attention must be paid to achieve proper flowability, disintegration, and dissolution.

5 | CONCLUSIONS

Even though the production of oral drug delivery systems by scaled-up ES has started to be explored only recently, the results are very encouraging so far, and it seems that there is real potential in translating the vast amount of laboratory-scaled studies performed hitherto into an industrial setting.

The different strategies to increase the productivity of ES have been reviewed followed by examples of fibrous oral drug delivery systems produced by scaled-up ES technologies. The potential of ES to improve the dissolution rate of poorly soluble APIs by amorphization has been shown. The technology can be a viable alternative to freeze drying and a suitable drying method for sensitive biopharmaceuticals—like proteins—as well. The options for downstream processing of the fibers to prepare tablets or capsules containing the electrospun drug substance was covered in this review as well. The information collected in this article shows that scaled-up ES technologies have a promising future in the pharmaceutical field, but research has to focus on further developments to transfer these technologies into industrial applications.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Panna Vass: Writing-original draft and writing-review and editing. **Edina Szabó**: Writing-original draft. **András Domokos**: Visualization; writing-original draft; and writing-review and editing. **Edit Hirsch**: Visualization and writing-original draft. **Dorián Galata**: Visualization and writing-original draft. **Balázs Farkas**: Writing-original draft. **Balázs Démuth**: Writing-original draft. **Sune Andersen**: Supervision and writing-review and editing. **Tamás Vigh**: Resources and writing-review and editing. **Geert Verreck**: Resources and writing-review and editing. **György Marosi**: Conceptualization; funding acquisition; validation; and writing-review and editing. **Zsombor Nagy**: Conceptualization; funding acquisition; supervision; writing-original draft; and writing-review and editing.

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