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Electrospinning for healthcare: recent advancements

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Electrospinning is a simple route to generate polymer-based fibres with diameters on the nano- to micron-scale. It has been very widely explored in biomedical science for applications including drug delivery systems, diagnostic imaging, theranostics, and tissue engineering. This extensive literature reveals that a diverse range of functional components including small molecule drugs, biologics, and nanoparticles can be incorporated into electrospun fibres, and it is possible to prepare materials with complex compartmentalised architectures. This perspective article briefly introduces the electrospinning technique before considering its potential applications in biomedicine. Particular attention is paid to the translation of electrospinning to the clinic, including the need to produce materials at large scale and the requirement to do so under Good Manufacturing Practice conditions. We finish with a summary of the key current challenges and future perspectives.

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Introduction

The electrospinning (ES) technique has attracted increasing attention for pharmaceutical applications in recent years.^{1–9}

A Web of Knowledge search for “electrospinning AND drug” (performed on 18/08/2020) reveals publication numbers rising year on year from the first reports in 2002 (two papers) through interest picking up by 2010 (115 publications) to 506 papers in

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2019. In essence, ES represents a novel pharmaceutical drying technology: it involves the use of electricity to solidify a polymer solution or melt.^{1,6} The inclusion of a drug in the liquid phase means that ES can be employed to generate solid dispersions (SDs) of drug-in-polymer.¹ The very rapid nature of the drying process (10^{-2} s, approximately) means that these tend to be amorphous in nature (amorphous solid dispersions, ASDs) and thus can accelerate dissolution rates and improve apparent solubility.¹ This is of great interest to the pharmaceutical industry, as increasing numbers (>75%) of emerging drug candidates fall in Biopharmaceutical Classification System Classes II and IV, and hence suffer from poor solubility.

There exist a range of other routes to preparing SDs and ASDs, with the most commonly applied being hot melt extrusion (HME), spray drying, and freeze drying.¹⁰⁻¹³ All these technologies have great utility in the pharmaceutical industry, and there are marketed products fabricated using all three. However, all have fundamental disadvantages associated with them. HME and spray drying apply heat, and thus are not

suitable for use with active ingredients that are thermally labile (e.g. biologics). Freeze drying can be used with biologics, but is a time consuming and costly process. All three methods are also energy inefficient, since electricity is used to generate heat (or to cool a chamber) and thereby generate an ASD, and at each conversion between energy types there is a loss of energy.¹ In ES, the application of electricity directly causes drying, which means that there is less energy lost and the process is more environmentally sustainable than other drying technologies.¹ Electrospun products also have a number of other benefits over those from HME, spray drying and freeze drying, which will be discussed in more detail below. For instance, the products of ES have morphologies very similar to the body's extracellular matrix, which means they are potentially highly suitable for tissue engineering applications. Until recently, implementation of ES on an industrial scale was hindered by limitations in the process scale-up. However, a number of high throughput ES technologies and instruments have emerged recently,² and hence the ES process is, in the authors' view, ripe



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Jinglei Wu received his PhD in Biomedical Engineering from the University of Texas at Arlington and Southwestern Medical Center joint program in 2017. He then worked as a scientist in the biotech company Progenitec Inc., before joining the Department of Bio-engineering at Donghua University as a lecturer in 2018. His research interests focus on naturally-derived materials for tissue engineering and regenerative medicine applications.



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materials. In the past ten years, Fenglei has participated in projects funded by the EU, EPSRC and CRUK, in which he pioneered the development of tissue-mimicking phantoms for diffusion MRI. These phantoms have won recognition in the MR community and have been used in ten world-leading university research groups.



Gareth R. Williams

Gareth is Professor of Pharmaceutical Materials Science and Head of Pharmaceutics in the UCL School of Pharmacy. He was educated at the University of Oxford, and then worked in science programme management and as a post-doctoral researcher before obtaining his first independent academic appointment at London Metropolitan University in 2010. He moved to UCL in 2012 as a lecturer, and was promoted to associate professor in 2016 and full professor in 2020. Gareth's research interests focus on the use of inorganic and polymer-based nanomaterials in biomedicine, as well as in the development of advanced analytical techniques.



solubility of the drug. This burst release is not a concern in the case of fast-dissolving formulations, but it can diminish the performance of systems designed for extended or delayed release. To overcome this issue, multi-fluid ES can be applied.

Multi-fluid electrospinning of small molecule drugs

Multi-fluid ES involves the processing of multiple fluids at the same time. Because the structure of the spinneret is propagated into the fibre product, it permits the production of fibres with a range of architectures, and can be used to prepare formulations with variable and tuneable API release profiles (Fig. 4).³⁶ It also significantly broadens the range of polymer solutions that can be processed by ES. In monoaxial spinning the polymer solution requires appropriate properties (*e.g.* viscosity) to be converted into fibres. If these properties are not suitable for ES (*e.g.* viscosity too low), then no fibres can be prepared. In contrast, in the multi-fluid experiment, it is possible to process solutions whose properties do not allow them to be individually electrospun (“unspinnable” fluids): so long as at least one of the fluids in the experiment is independently spinnable, it is generally possible to generate a fibre product. Thus, a solution with low viscosity can be converted into a solid fibre product in coaxial ES so long as the companion solution is electrospinnable.

While in theory any number of fluids can be processed, at present the state of the art is limited to two or three fluids, with a few reports of four-fluid ES.³⁷ With two solutions, the needles can be arranged concentrically (one nested inside another, or coaxial spinning), giving core/shell products.³⁸ Aliter, the two fluids could be dispensed in a side-by-side configuration, resulting in Janus fibres (with two different sides). A three-layer concentric spinneret can be used to prepare triaxial fibres, or alternatively more complex needle arrangements can be implemented to generate for instance core/shell fibres with a Janus core.

The apparatus required for multi-fluid ES is essentially the same as the monoaxial apparatus displayed in Fig. 2, except

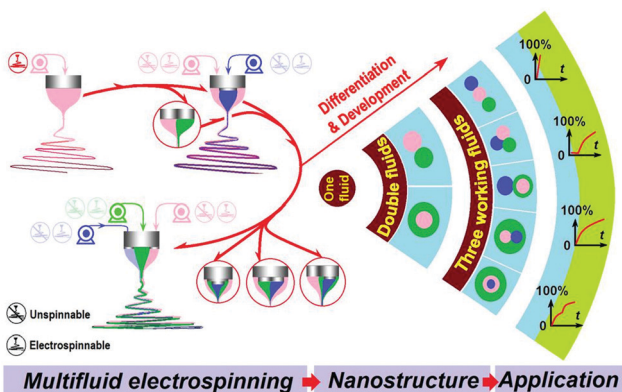


Fig. 4 A schematic diagram showing the possible arrangements of liquids in multi-fluid ES, the nanostructures which can be produced as a result, and the potential drug release profiles.

that multiple syringe pumps are typically required (one to drive each working fluid) and the spinneret architecture is more complex. The properties of the working fluids and operational parameters need more careful consideration for multi-fluid ES, however.³⁹ The volatility and drying rates of the different solutions is important, as are the relative flow rates.

The multiple-compartment structures produced by multi-fluid ES have several benefits for developing novel DDSs. The components, compositions, and the spatial distribution of APIs within the materials can be tailored to yield sophisticated drug release profiles (*e.g.* immediate release, delayed release, sustained release and multiple-phase release; see Fig. 4). The core/shell structures of fibres from coaxial electrospinning have been widely used to prevent the initial burst release commonly experienced with monolithic materials produced from monoaxial spinning. This is achieved using a simple polymer solution as the shell, while the core comprises a drug/polymer blend solution. The resultant fibres thus have a blank polymer shell, and there is no contact between the release medium and the API-loaded compartment on first immersion. The drug release rate is controlled by the speed at which the shell compartment dissolves or degrades, or by the rate of drug diffusion through the shell. This approach has been demonstrated in a number of studies, for instance that of He *et al.* where core/shell fibres of poly(lactide) (PLA) were prepared with the antibiotic tetracycline hydrochloride confined to the core.^{14,40}

Core/shell fibres have also been used to provide delayed release to avoid release in the stomach and target the drug to the small intestine (using a pH-sensitive polymer shell).^{41,42} Multifunctional materials can be prepared, with different APIs in the core and shell compartments⁴³ or with flavour enhancers or surfactants added to the shell to improve palatability or permeation of the drug through biomembranes.^{44,45} The latter might be expected to be more effective than including the flavor enhancer in a monolithic fibre, because the shell of a core/shell formulation will dissolve before the core, and hence the flavor enhancer is freed into the mouth before the unpleasant tasting drug. Triaxial systems have been less explored owing to the complexity of fabrication, but there are a number of studies in the literature exploring these.^{46,47} The increased control over the fibre architecture which results can yield highly desirable APIs release profiles. For instance, Yu *et al.* reported triaxial ethyl cellulose/ketoprofen fibres with varied concentrations of API in the three fibre compartments, and showed that zero-order release could be obtained (Fig. 5).⁴⁸ This is highly sought after in pharmaceutical science, but very challenging to achieve. Alternatively, using a hydrophilic exterior polymer with a hydrophobic middle layer has been found to allow the fibres to interact favourably with cells while still releasing a drug cargo over a prolonged period of time.⁴⁹

There is also relatively little work in the literature looking at Janus fibres for pharmaceutical applications, but there are potential benefits of these over the more widely explored core/shell structures. With Janus fibres, the two sides are both in contact with the release milieu, which could be advantageous to, for instance, release two different drugs in the same location but at different rates, or to tune API release profiles.⁵⁰



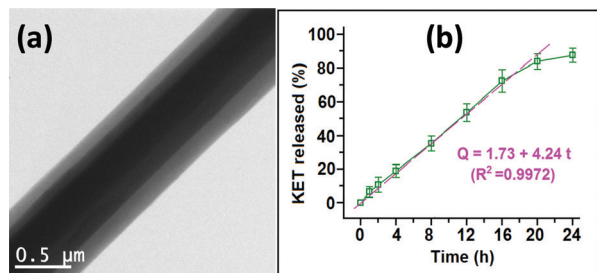


Fig. 5 The triaxial fibres prepared by Yu *et al.* (a) Transmission electron microscopy image, and (b) the resultant zero-order drug release profile. Adapted with permission from ref. 48 (Yu *et al.*, 2015). Copyright 2015 American Chemical Society.

The complex nanostructures which can be prepared by multi-fluid ES are still in the very early stages of exploration, and there are extensive possibilities for future developments.⁵¹ The diversity of materials which can be produced, in combination with the ability to process unspinnable liquids, means that a wide range of multifunctional formulations are expected to emerge in the coming years.

Electrospinning and proteins

Protein-loaded biomaterials are generating considerable interest due to the growing importance of immunotherapy and tissue engineering in modern medicine.^{52,53} The complex and fragile structures of many therapeutic proteins require advanced delivery methods and careful optimisation of formulation and manufacturing conditions.⁵⁴ ES offers a simple solution for the fabrication of protein-loaded materials. Multiple approaches have been proposed for the incorporation of therapeutic proteins in electrospun scaffolds. These can be broadly divided into post-fabrication surface functionalisation, emulsion ES, and coaxial ES.

Physical adsorption is often used to attach proteins to polymeric surfaces. This simple approach does not require multi-step treatments in harsh conditions and relies solely on relatively weak electrostatic, van der Waals and hydrophobic interactions.⁵⁵ The 3D-structure of ES fibres provides a large surface area for protein adsorption. The immediate release of bioactive agents which results from weak adsorption to the surface is desired for certain applications where instant biological action is needed. For example, Xia and Lv⁵⁶ described the dual delivery of growth factors for peripheral nerve regeneration using PLA nanofibres. Recombinant human nerve growth factor (NGF) was loaded into the core of the fibre, and the surface functionalised with human vascular endothelial growth factor (VEGF) by physical adsorption. The resultant material was able to effectively support nerve regeneration in rats *in vivo*.

Chemical conjugation of bioactive molecules onto the fibre surface *via* rigid covalent bonding can immobilize them on the surface for an extended period of time. There are a range of routes to such functionalisation, for instance using polydopamine chemistry.^{57,58} In a 2019 study, Liu *et al.*⁵⁹ applied this

method to conjugate osteogenic growth peptide to PLA nanofibres, which led to improved cell adhesion and proliferation (Fig. 6).

While monoaxial ES can be employed to generate fibres on which proteins are subsequently attached, it is generally not suitable for preparing fibres with the protein incorporated inside the structure. This is because it uses volatile organic solvents, which tend to cause damage to the protein structure and diminish therapeutic efficacy. This can be avoided using emulsion or multi-fluid ES. In the former process, a core-shell nanofibre structure is formed by ES of an emulsion formed from an aqueous phase (containing protein) and an organic phase (polymer).⁶⁰ This is a simple approach, but the protein-polymer blend must be carefully optimized to ensure no loss of bioactivity resulting from accidental exposure of biomolecule to the organic solvent. A non-ionic surfactant is often incorporated in the formulation to reduce the contact of the protein with organic solvents.⁶¹ Frizzell *et al.* used surfactant-assisted emulsion ES to generate enzyme-loaded electrospun Eudragit fibres intended for oral delivery.⁶² These could prevent protein release in the pH conditions of the stomach, thereby avoiding the risk of enzyme degradation and targeting release to the small intestine.

In coaxial ES, the two working fluids are physically separated until they exit the spinneret, and hence this approach too can minimise protein exposure to organic solvent. The resulting fibre usually holds the protein in the core, with the polymer shell controlling the release rate of the cargo. Angkawinitwong *et al.* have exploited this method for the fabrication of bevacizumab-loaded poly(ϵ -caprolactone) (PCL) fibres for the treatment of age-related vascular macular degeneration in the

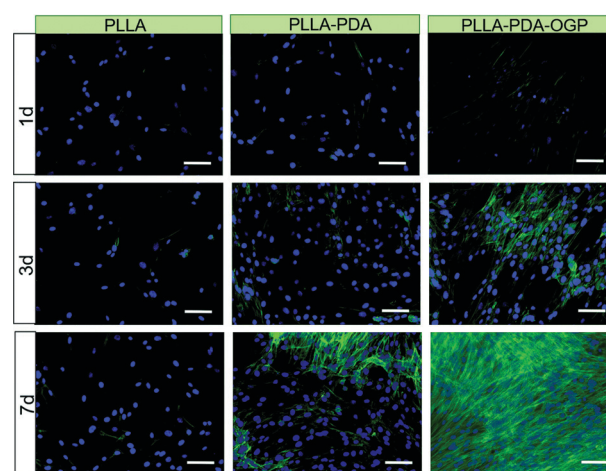


Fig. 6 The use of polydopamine chemistry to facilitate cell growth on ES fibres. Scale bar: 100 μ m. Fibres were prepared from poly(L-lactide) (PLLA), and then immersed in polydopamine to yield PLLA-PDA fibres. These were further immersed in a solution of the osteogenic growth peptide (OGP) to conjugate the peptide and generate PLLA-PDA-OGP. Cell nuclei are blue and the intracellular protein F-actin is green. The presence of OGP on the fibre surface clearly encourages cell growth. Reproduced from ref. 59 (Liu *et al.*, 2019) under the terms of the Creative Commons CC BY 3.0 license. Published by The Royal Society of Chemistry.



as closely as possible, electrospun grafts with multiple layers have been generated. Surface functionalization can also be applied to prevent blood clots forming and aid remodeling of vascular grafts.⁹⁷ Many studies have reported successful regeneration of blood vessels in animal models, but ES vascular grafts for humans are not yet available.

ES tubular scaffolds have also shown potential in peripheral nerve regeneration, but it remains challenging to achieve desired physiological functions such as the transmission of electrical stimuli (since the polymers used for ES are generally not electrically conductive). The inclusion of conductive polymers is one route to potentially circumvent this problem, but can also compromise biological performance. As an alternative, a conductive nerve conduit was prepared by *in situ* redox reactions of graphene oxide on the surface of ES scaffolds.⁹⁸ These exhibited promising mechanical properties and electroactivity, induced nerve cell differentiation, and guided peripheral nerve regeneration to a comparable level as current gold standard autografts in a rodent model. The incorporation of drugs into the fibres to stimulate nerve growth has also been shown to be beneficial.⁹⁹

In general, fibre scaffolds produced by ES contain relatively densely packed fibres, and it can be difficult for cells to penetrate into the matrix, therefore preventing the complete regeneration of the desired tissue. A novel ES technique was recently introduced to convert the as-spun nanofibres into individual short fibres that can be reconstructed to highly porous and elastic aerogels.¹⁰⁰ This technique essentially involves the homogenization of the fibre mat produced by ES, and increases the capacity of ES nanofibres in tissue engineering because the resultant porous scaffolds support cell infiltration and proliferation, which drives robust tissue remodeling and regeneration. For instance, ES aerogel scaffolds induced osteogenic differentiation of mesenchymal stem cells and promoted cranial bone regeneration in a rat model.^{101,102} They have also been shown to enhance cartilage repair in a rabbit model.¹⁰³ The aerogels can be crafted into a range of 3D shapes suitable for use in different tissue engineering applications.¹⁰⁴ It is also possible to directly combine 3D printing and electrospinning to generate 3D structures.^{93,104,105} The interested reader is directed to two recent reviews for more information.^{93,104}

While ES scaffolds with porous structures can be desirable, scaffolds with densely packed fibres are also beneficial in some scenarios because they effectively resist cell infiltration and tissue ingrowth. ES PCL/gelatin membranes have for instance been used as a physical barrier to prevent cardiac operative adhesions (a type of scar tissue arising after cardiac surgery) in a rabbit model.¹⁰⁶ The incorporation of ibuprofen or siRNA into the fibres was also found to be beneficial here.^{107,108} In other work, MgO loaded ES fibres have been found to have significant promise in periodontal tissue regeneration.¹⁰⁹

Scale-up and clinical translation

The above sections clearly indicate the great potential of electrospinning in a wide range of biomedical applications.

For ES fibres to achieve this potential, there is a need to move the experiment out of the lab and towards the clinic. In some cases, this involves the miniaturisation of equipment to allow it to be used at the point of care. To this end, there has been much recent work looking to develop portable ES apparatus for wound healing, with notable successes in this area.¹¹⁰ More commonly, the opposite is required: the low-throughput (*ca.* 0.5–20 mL h⁻¹) benchtop electrospinning process needs to be scaled up to produce industrial quantities of materials. There are a number of approaches that can be used to achieve this, the simplest of which is to dispense fluid through multiple needles at the same time.¹¹¹ However, since all the needles bear the same charge and are in close proximity, the electrical field around each needle interferes with its neighbours.¹¹² Blocking of the needles can also be a challenge. A number of researchers have sought to overcome these issues.^{112,113} For instance, increasing the distance between the nozzles and the collector can compensate for instabilities in the electric field caused by adjacent needles. Using such multi-needle approaches, industrial scale amounts of material can be produced (*e.g.* Bioinicia's facilities can generate more than 2.2 million m² of fibres per year).¹¹⁴

An alternative route to high-throughput is the needleless approach. This generates Taylor cones directly from the surface of a polymer solution (using a much higher potential difference than in a standard ES experiment), and these spontaneously arrange themselves in the most thermodynamically stable configuration possible.¹¹⁵ Commercial apparatus such as the NanoSpider™ equipment from Elmarco is available and can generate fibres at throughput of tens of millions of m² per year.¹¹⁶ Working with a large exposed surface area of solvent carries its own hazards, given the volatility and flammability of many solvents used in ES, and to avoid this researchers have applied a number of modifications to permit

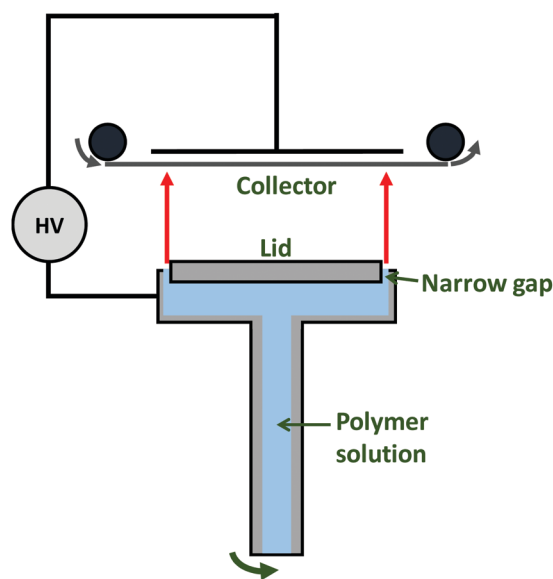


Fig. 10 Schematic diagram of the corona electrospinning apparatus developed by Molnar *et al.*¹¹⁷



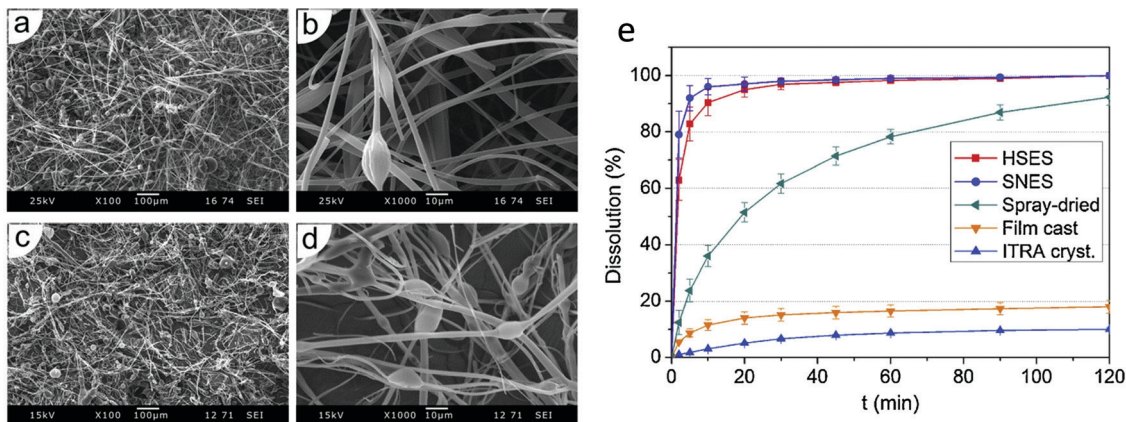


Fig. 11 Data obtained using monaxial and high speed corona electrospinning for the preparation of poly(vinyl pyrrolidone/vinyl acetate)/itraconazole (ITRA) fibres. Scanning electron microscopy images of (a) and (b) the monoxial fibres, and (c) and (d) the high-speed fibres are shown together with (e) dissolution profiles of high-speed (HSES) and monoxial ES (SNES) fibres, compared with analogous spray-dried or film-cast formulations and the raw material. Adapted with permission from ref. 119 (Nagy *et al.* 2015). Copyright Elsevier.

only a small amount of polymer solution to be exposed at any one time.²

One promising needleless modality is the corona ES method pioneered by Molnar and co-workers.¹¹⁷ This uses a rotating spinneret, to which polymer solution is fed from a reservoir. A narrow gap at the edge of the spinneret permits Taylor cones to form and fibres to be generated while the majority of the polymer solution remains covered (Fig. 10). Amendments to the collector are also required for high-throughput electrospinning, and in most cases a conveyor-belt type collector is used (Fig. 10). In addition to the risks of fire from the large volumes of solvents used in high-throughput ES, environmental considerations are also important since there are toxicities associated with many common ES solvents.

A number of researchers have produced drug-loaded ES fibres on the large scale using the needleless approach. For instance, fibres have been prepared made of poly(vinyl alcohol) loaded with the antiretroviral drug tenofovir (yielding up to 7.7 g of product per hour),¹¹⁸ or poly(vinyl pyrrolidone/vinyl acetate) incorporating the antifungal itraconazole (450 g of product per hour).¹¹⁹ Increasing the throughput rate is generally observed to lead to thicker fibres with larger diameters. It also reduces the homogeneity of the fibres, leading to larger variation in fibre diameters and more bead-on-string type morphologies (Fig. 11a–d). However, the functional performance is not affected to any significant extent by moving to a high-speed ES process (Fig. 11e). It has been shown that the products of high-throughput ES can be processed into tablets,¹²⁰ and remain stable upon storage.¹²¹ It has even proven possible to integrate the steps of drug synthesis, ES, and post-processing into tablets in a single end-to-end process.¹²²

Finally, we should note the importance of being able to prepare materials in GMP conditions for ES fibres to be able to move forward into the clinic. This requires robust quality control processes and working in clean-room conditions, but is eminently possible (although resource-intensive). There are studies in the literature which have generated ES materials to

these stringent quality standards,¹²³ and the company Bioinicia have a GMP-standard ES facility¹¹⁴ which has been used to prepare materials for clinical trials of the Rivelin patch formulation (to treat oral lichen planus) developed by Afyx.^{124,125} The results from these trials are very promising, which bodes extremely well for the future of ES formulations in the clinic.

That said, there are a number of challenges which must be overcome before electrospun products are ready for the clinic. More work is required to develop robust and reproducible protocols for production, and the number of studies looking at the high-throughput production of fibres by ES is still limited. Often in the literature toxic solvents are used in electrospinning, and for clinical applications it will be necessary to move to more benign solvents, and/or put in place robust procedures to ensure that all solvent is exhausted after spinning. Handling large volumes of toxic or flammable solvents in high-throughput processes is also difficult, and requires more work to ensure this is done safely and without damage to the environment. Ideally, solvent would be recycled back into the system to minimise waste. Beyond this, quality control standards and processes will be needed to ensure products with highly reproducible characteristics and which are safe and effective for patients.

Conclusions and outlook

The electrospinning (ES) process is a powerful route for the generation of polymer-based fibres with diameters on the nano-to-micron-scale. A wide variety of functional components can be incorporated into these fibres, including small molecule drugs, proteins and cells. Multiple fluids can be processed simultaneously, yielding fibres with core/shell, Janus or more complex architectures. ES fibres can be employed for drug delivery (for instance to accelerate dissolution rate, target release to a particular part of the body, or prolong release for sustained



treatment of a condition). They may furthermore be used for the diagnosis and imaging of disease, for simultaneous treatment and diagnosis (“theranostics”), and to regenerate damaged tissue such as nerves or bone. It is now possible to produce ES fibres on an industrial scale, and in GMP conditions. At least one ES product is now in clinical trials. In the view of the authors, after some years in the wilderness the ES technology is now on the cusp of making the leap into the clinic. In addition, there have recently been exciting developments in preparing short fibres and aerogels from electrospun products, in 3D electrospinning, in the development of increasingly complex architectures from multi-fluid processes, and in high-throughput production. These innovations are expected to continue into the future, leading to ever more tuneable and effective formulations.

Author contributions

All authors contributed to undertaking detailed literature research and the writing of this manuscript, with lead contributions to sections as follows: Karolina Dziemidowicz – electrospinning and proteins; Qingqing Sang – electrospinning of small molecule drugs; Jinglei Wu – tissue engineering; Ziwei Zhang – theranostic formulations; Fenglei Zhou – diagnosis and imaging; Jose M. Lagaron – scale up and clinical translation; Xiumei Mo – tissue engineering; Geoff J. M. Parker – diagnosis and imaging; Deng-Guang Yu – multi-fluid electrospinning of small molecule drugs; Li-Min Zhu – electrospinning of small molecule drugs; Gareth R. Williams – compilation of manuscript, introduction, conclusions and perspectives. All authors additionally reviewed and approved the final version of the manuscript.

Conflicts of interest

JML is founder of the spin-out company Bioinicia SL, which has commercial interests in the GMP manufacture and scale-up of electrospun formulations.

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