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Alternative nanofibre fabrication approaches

6.1 Introduction

The previous chapters have all focused on electrospinning as the means of fibre formation, since this is the technique which has to date received by far the most research attention. There exists a range of other, less explored, technologies for fibre production, however, and these will all be discussed briefly in the context of drug delivery in this chapter. Further details on the principles of many of these techniques can be found in recent reviews by Luo *et al.*¹ and Qi and Craig.²

6.2 Alternating current electrospinning

Electricity comprises a flow of electrons (negatively charged subatomic particles). In direct current (DC; used for the vast majority of electrospinning work) the electrons flow in one direction continually. It is also possible to have alternating current (AC), which is used to power most electrical devices in the home. AC involves a periodic change in the direction of current flow: that is, the electrons first flow in one direction and then switch to flow in the reverse direction. The switch between directions is repeated many times per second and is known as the frequency of the AC. Using an AC power supply rather than the conventional DC supply was first shown to generate polymer-based nanofibres in 2004.³

The experimental set-up for AC electrospinning is similar to that for the DC process, but it does not require a grounded collector. Because

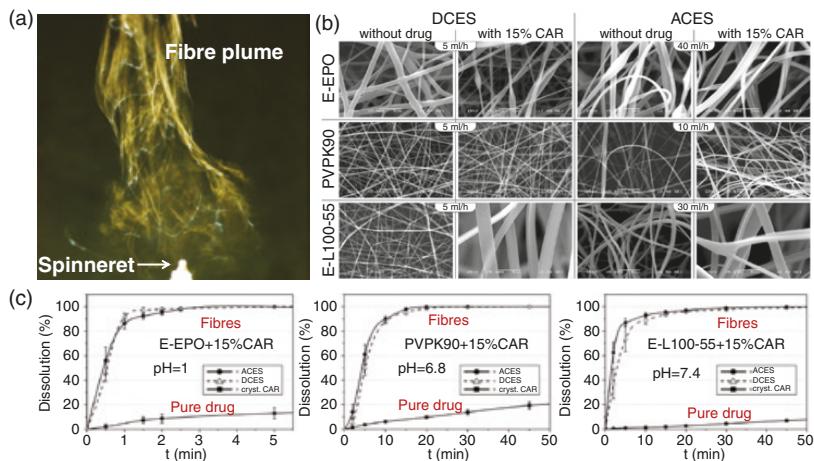


Figure 6.1 Alternating current electrospinning for fibre production.
 (a) The plume of fibres produced; (b) fibres produced from direct current electrospinning (DCES) and alternating current electrospinning (ACES) (E: Eudragit; CAR: carvedilol); (c) dissolution profiles for the fibres. (Adapted with permission from Balogh, A.; Cselko, R.; Demuth, B.; Verreck, G.; Mensch, J.; Marosi, G.; Nagy, Z. K. ‘Alternating current electrospinning for preparation of fibrous drug delivery systems.’ *Int. J. Pharm.* 495 (2015): 75–80. Copyright Elsevier 2015.)

the current alternates, the fibres produced at one instant in time carry a positive charge, while those generated shortly thereafter have a negative charge. The positive and negative fibres thus discharge on each other, which results in an aerogel plume of fibres, as depicted in Figure 6.1(a). The frequency of the AC current determines whether charge carriers of one polarity have sufficient time to charge the solution and result in spinning. The optimal AC frequency is material-dependent and typically in the range of 50 Hz–1 kHz.⁴

The AC approach has been explored for the fabrication of drug-loaded fibres in a few recent studies. In one, Balogh *et al.* undertook a direct comparison of fibres prepared by DC and AC spinning.⁵ They used the beta-blocker carvedilol as a model drug, and fibres were generated using three different polymers: Eudragit EPO, a cationic copolymer soluble below pH 5.0; Eudragit L100-55, an anionic polymer soluble above pH 5.5; and the neutral polymer poly(vinyl pyrrolidone) (PVP). It was found that fibres could be generated with all three polymers from both types of spinning (Figure 6.1(b)), but that it was possible to use much faster flow rates in the AC process. With DC spinning, a maximum

flow rate of 5 ml h⁻¹ could be achieved, whereas with AC this could be increased to up to 40 ml h⁻¹. All fibres, from both processes and made from all polymers, existed as amorphous solid dispersions. The drug release profiles were studied, and the AC and DC fibres were found to be indistinguishable in their performance ([Figure 6.1\(c\)](#)).

The same team have also compared AC and DC electrospinning of blends of hydroxypropylmethylcellulose (HPMC) and poly(ethylene oxide) (PEO) with the poorly water-soluble diuretic spironolactone.⁶ Both HPMC and PEO alone could be processed by the DC approach. In contrast, AC electrospinning of HPMC led to a mixture of droplets and fibres, and high-molecular-weight PEOs did not yield any solid products at all in the AC method. Selecting appropriate blends of the two polymers, however, permitted high-quality fibres to be formed via AC spinning.

AC processing of HPMC or PEO with spironolactone also proved to be problematic, but again with the right mix of HPMC and PEO drug-loaded fibres could be generated. These were able to accelerate the dissolution rate of the drug, even at loadings of up to 40% w/w. The AC-generated fibres were found to be several orders of magnitude thinner than the DC electrospun fibres despite the flow rate being three times faster in the AC process.

Similar observations have been reported using HPMC acetate succinate (HPMCAS) and spironolactone.⁷ HPMCAS could not be processed by either DC or AC electrospinning; the addition of PEO permitted fibres to be produced with the DC approach, but not using AC, and the addition of an ionic surfactant or salt was required to produce high-quality fibres with AC spinning. As with HPMC, the HPMCAS fibres led to a significant enhancement in the dissolution rate.

It is thus clear that AC electrospinning is similarly effective to the DC approach in producing drug delivery systems. Although its use in this regard is in its infancy, given the fact it allows higher throughput than the DC technique, it seems certain that this is an approach which is likely to receive much more attention in the coming years.

6.3 Melt electrospinning

Another variant of electrospinning which has attracted some attention in the drug delivery sphere is the melt process. This is discussed in detail in a recent review.⁸ In brief, the process is analogous to the solution electrospinning discussed in previous chapters, but in place of a

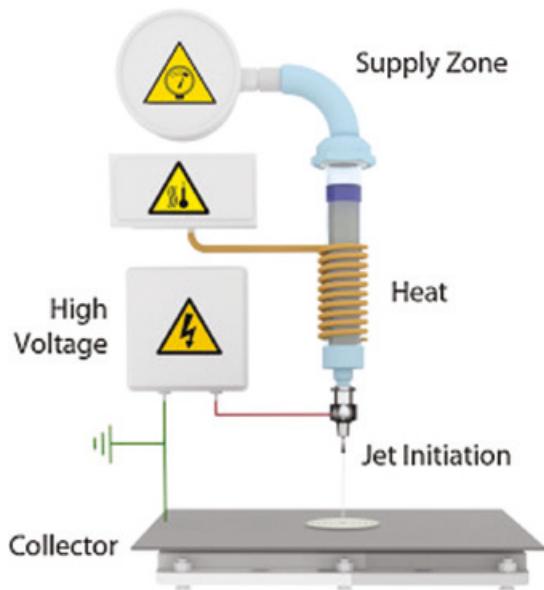


Figure 6.2 The apparatus used for melt electrospinning. (Reproduced with permission from Brown, T. D.; Dalton, P. D.; Hutmacher, D. W. ‘Melt electrospinning today: An opportune time for an emerging polymer process.’ *Prog. Polym. Sci.* 56 (2016): 116–166. Copyright Elsevier 2016.)

polymer solution a melt is used. This adds some complexity to the process, because the syringe and spinneret must be heated to maintain the polymer in its liquid state. Further, the elevated temperature can potentially lead to drug degradation, since many drugs are thermally labile. The fibres produced in melt spinning are typically found to have larger diameters than those from the solution route due to the significantly higher viscosity of a polymer melt than its solution form. The apparatus used is depicted in [Figure 6.2](#).

Despite these apparent disadvantages, there are a number of attractive aspects of the melt spinning process, not least the fact that it obviates the need to handle large volumes of volatile solvents. This both renders the process safer, particularly if it is to be performed on the larger scale, and precludes any solvent contamination in the products.

The first report of a melt electrospun drug delivery system came from Nagy and co-workers, who prepared melt-spun fibres of Eudragit

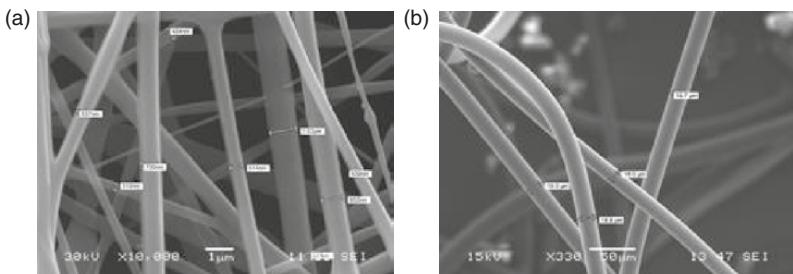


Figure 6.3 Scanning electron microscopy images of Eudragit E / carvedilol fibres prepared by (a) solution and (b) melt electrospinning. (Reproduced with permission from Nagy, Z. K.; Balogh, A.; Dravavolgyi, G.; Ferguson, J.; Pataki, H.; Vajna, B.; Marosi, G. ‘Solvent-free melt electrospinning for preparation of fast dissolving drug delivery system and comparison with solvent-based electrospun and melt extruded systems.’ *J. Pharm. Sci.* 102 (2013): 508–517. Copyright Elsevier 2013.)

EPO loaded with carvedilol.⁹ The drug and polymer were melted and mixed to form a homogeneous solid mixture prior to spinning, and then processed as in a solution experiment but with both the syringe and spinneret heated. The melt fibres were much wider than analogous systems processed through solution spinning, with those from melt processing having diameters of 5–30 μm, as compared to 300–1000 nm for the solution-spun fibres (Figure 6.3). The drug was completely amorphously dispersed in the fibres regardless of the processing route. This is as expected for solution spinning, and in the melt case was thought to be because the experiment was carried out above the melting point of carvedilol. The melt fibres freed their drug loading faster than the solution-spun analogues, despite the much larger surface area of the latter. The authors ascribed this to the fact that the melt fibres had a loose non-woven structure, whereas those prepared by solution spinning were more tightly packed (Figure 6.3).

This work has been built on to blend plasticisers with the polymer Eudragit E and carvedilol active ingredient.¹⁰ The plasticisers triacetin, Tween 80 and polyethylene glycol were all investigated with the goal of reducing the melting point of the polymer/drug blend and thereby permitting lower temperatures to be used for spinning. This should reduce the likelihood of any degradation occurring. High-performance liquid chromatography data obtained on dissolved fibres revealed that the addition of plasticisers clearly reduced the amounts of carvedilol degradation products present after melt spinning.

A direct comparison of poly(ϵ -caprolactone) (PCL) fibres generated by the melt and solution-spinning approaches has been reported by Lian and Meng.¹¹ These authors prepared curcumin-loaded fibres of around 4 μm in diameter using both techniques. They found that there was a greater tendency for the curcumin to crystallise using the solution route (a result of its low solubility in the solvent used for spinning). The melt fibres led to a reduced burst release and a slower release rate. These findings were attributed to the solution-spun fibres having a porous structure, which permitted both water ingress and the incorporated curcumin to diffuse out of the polymer matrix.

Melt electrospinning typically generates micron-size fibres. In a recent effort, however, highly uniform and precise deposition of PCL nanofibres ($817 \pm 165 \text{ nm}$) was achieved using a method known as *melt electrospinning writing*.¹² This combines melt electrospinning with additive manufacturing (three-dimensional (3D) printing) technology, using a computer-controlled extruder moving on a translational stage to build a 3D structure layer by layer. The 3D fibrous architecture produced allowed efficient *in vitro* proliferation of primary human mesenchymal stromal cells. The melt electrospinning writing technology can produce regular 3D morphologies in a highly controllable and reproducible fashion, and is currently being explored for a range of tissue-engineering applications.

Although melt electrospinning has received much less research interest than the solution process, it appears to be equally as flexible in terms of handling multiple fluids, and coaxial melt spinning has been reported.¹³ The initial melt spinning experiment is perhaps harder to establish than the solution route, but it is clear that this approach has a great deal of unexplored potential in the development of drug delivery systems.

6.4 Centrifugal spinning

Centrifugal spinning employs a rotating polymer source to generate fibres. Several centrifugal methods can generate nanofibres. These include Forcespinning, which employs rotary speed of above 2000 revolutions per minute (rpm),¹⁴ electrocentrifugal spinning,¹⁵ which combines a strong electric potential (as in electrospinning) with centrifugal force, and pressurised gyration, which adds high pressure ($> 10 \text{ kPa}$) to centrifugal spinning to enhance fibre formation (see section 6.8).¹⁶

These approaches can be applied to polymer solutions and emulsions, and if the source can be heated also to a polymer melt

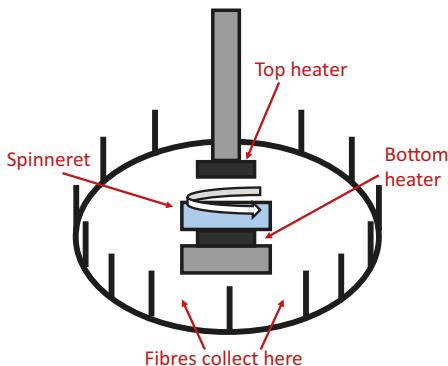


Figure 6.4 A schematic diagram of the apparatus used for centrifugal spinning. (Adapted from Zander, N. E. ‘Formation of melt and solution spun polycaprolactone fibers by centrifugal spinning.’ *J. Appl. Polym. Sci.* 132 (2015): 41269¹⁸.)

(Figure 6.4).¹⁷ This technique has received some attention in the context of drug delivery. For instance, Zander prepared PCL fibres using both the solution and melt variants of the centrifugal technique.¹⁸ This author employed spinning speeds in the range of 3000–18,000 rpm, yielding fibres of ca. 10 µm in diameter. PC12 neuron cells could be successfully grown on the fibres, demonstrating that they have potential in nerve tissue engineering.

In other work, centrifugally spun PCL/PVP fibres containing the antibiotic tetracycline have been produced from a methanol/chloroform solution at 2000 rpm.¹⁹ These were sub-micron in their diameters, and highly aligned. The rate of drug release could be tuned by varying the PCL/PVP ratio in the fibres, and the fibres were found to be effective in inhibiting bacterial growth. Core/shell fibres for the delivery of growth factors have further been reported from centrifugal spinning of a water-in-oil emulsion, with PCL dissolved in the oil phase.²⁰

Fibres have also been made using a melt process with sucrose (a sugar dimer) loaded with a range of poorly water-soluble drugs, including olanzapine (an antipsychotic medicine) and piroxicam (a non-steroidal anti-inflammatory).²¹ The fibres were 10–15 µm in diameter, and the dissolution rate of the drugs enhanced after fibre formation.

Since the centrifugal spinning approach is a simple one which allows relatively large-scale production of fibres,²² it appears to have much promise in the drug delivery field. It can also be coupled to electrospinning, with both centrifugal and electrical forces applied

simultaneously to drive solvent evaporation.¹⁵ Such centrifugal electrospinning uses the same equipment as the standard centrifugal process but additionally applies a high voltage between the rotating spinneret and the collector. It has been reported to lead to significantly higher throughput than standard electrospinning,²³ and to produce highly aligned fibres.^{23b, 24} Centrifugal electrospinning has further been demonstrated to have potential in the production of drug delivery systems, with a recent report of PVP fibres loaded with the antibiotic tetracycline hydrochloride.²⁵ Production rates of up to 120 g h^{-1} could be realised.

6.5 Solution blowing and melt blowing

A pressurised gas can be exploited to produce nanoscale fibres, starting either with a polymer solution in a technique known as solution blowing or from a molten polymer source (melt blowing). The experimental apparatus used is similar to electrospinning, in that a polymer solution (or melt) is expelled through a needle (spinneret) at a controlled rate. The spinneret is surrounded by an outer nozzle which applies pressurised gas to the fluid being expelled, as illustrated in [Figure 6.5](#).²⁶

A few studies have explored solution blowing in drug delivery, with the first such work being from Oliveira *et al.* in 2013.²⁷ These authors prepared poly(lactic acid) (PLA) fibres loaded with the hormone progesterone, which can be used to regulate the reproductive cycle in livestock. Fibres were produced from solutions with 6% w/v PLA and between 0 and 8% w/v progesterone ([Figure 6.6\(a\)](#)). The PLA is semi-crystalline both before and after processing, while the drug is amorphous post-spinning. The fibres behave very similarly in terms of their release behaviour, regardless of the amount of drug loaded ([Figure 6.6\(b\)](#)).



Figure 6.5 The apparatus used for solution blow spinning or melt blowing. (Adapted from Souza, M. A.; Sakamoto, K. Y.; Mattoso, L. H. C. 'Release of the diclofenac sodium by nanofibers of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) obtained from electrospinning and solution blow spinning.' *J. Nanomater.* 2014 (2014): 129035.)

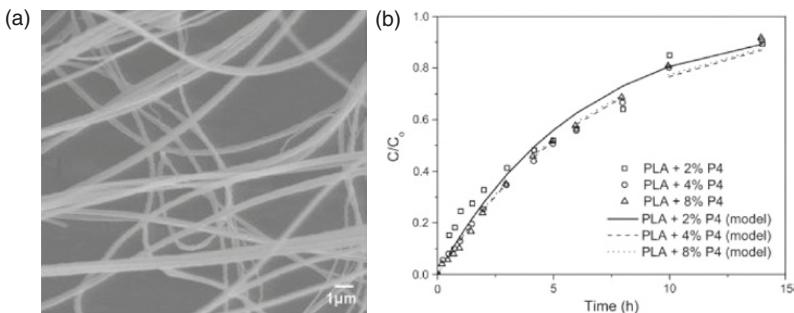


Figure 6.6 Progesterone-loaded poly(lactic acid) (PLA) fibres prepared by solution blowing. (a) A scanning electron microscopy image of fibres prepared with 6% w/v PLA and 4% w/v progesterone; (b) drug release profiles for fibres prepared from solutions of 6% w/v PLA and 2, 4 or 8% progesterone (P4). (Reproduced with permission from Oliveira, J. E.; Medeiros, E. S.; Cardozo, L.; Voll, F.; Madureira, E. H.; Mattoso, L. H.; Assis, O. B. ‘Development of poly(lactic acid) nanostructured membranes for the controlled delivery of progesterone to livestock animals.’ *Mater. Sci. Eng. C* 33 (2013): 844–849. Copyright Elsevier 2014.)

A study comparing electrospun and solution-blown fibres of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) loaded with sodium diclofenac has also been reported.²⁶ The drug-loaded fibres were slightly larger in diameter when generated by electrospinning, and the size uniformity was higher through solution blowing. In general there was a greater amount of burst release seen with the electrospun fibres, but otherwise there were no clear trends in the drug release data.

Solution-blown fibres have additionally been created loaded with oil extracted from the medicinal plant *Copaifera* sp., which is often explored for antimicrobial purposes.²⁸ These materials were constructed from a blend of the polymers PLA and PVP, and were around 1 μm in diameter. An increased PVP content was found to result in increased antibacterial activity after 24 h.

The melt blowing process has also received some attention in the pharmaceutical setting, and the fibres produced compared with those from both solution and melt electrospinning.²⁹ Marosi’s team generated formulations from a vinylpyrrolidone–vinyl acetate copolymer, employing poly(ethylene glycol) (PEG) as a plasticiser and carvedilol as a model drug. All three methods led to fibres, with the solution electrospun fibres narrowest (at ca. 2 μm in diameter), followed by the melt-blown (10 μm) and melt-spun (50 μm) products. Carvedilol was rendered into the

amorphous physical form by all three processing techniques, and all the formulations were able to accelerate the drug dissolution process. The melt-blown and melt electrospun systems led to the fastest release, with almost identical release profiles, while the solution-electrospun fibres freed their drug cargo somewhat more slowly.

A variant of the solution-blowing technique has been applied to the processing of living cells (in this setting it has been referred to as *biothreading*).³⁰ Using a pressurised coaxial needle with the exterior fluid comprising a viscous polydimethylsiloxane solution and an aqueous cell suspension in the core, cells can be processed into scaffolds with no noticeable loss in viability.

6.6 Electroblowing

Electrospinning and melt/solution blowing can be combined in a process known as electroblowing. This employs both electricity and a gas flow to aid fibre elongation and solidification. The experimental apparatus uses a similar spinneret to that in Figure 6.5, and in addition to the gas flow a potential difference is applied between the spinneret and the collector. This technique has been shown to have significant potential in medical applications: in 2014, Jiang *et al.* applied electroblowing *in vitro* and *in vivo* to deliver a homogeneous and continuous layer of a medical glue to stop bleeding during liver resection.³¹

More recently, Balogh *et al.* prepared fibres of 2-hydroxypropyl- β -cyclodextrin loaded with sodium diclofenac.³² They found that when electrospinning this system, very frequent clogging of the spinneret occurred. Electroblowing overcame this issue and additionally allowed faster flow rates to be used, increasing the amount of material that could be produced. However, the uniformity of the fibre products was compromised, with more ‘beads-on-string’ type morphology seen with the blown products. In both cases, the fibres comprised amorphous solid dispersions with no crystalline drug evident. The electroblown fibres dissolved a little more slowly than those from electrospinning, but still much more rapidly than a physical mixture of drug and cyclodextrin.

A subsequent study using Eudragit E and itraconazole (an antifungal active pharmaceutical ingredient) also found that a faster flow rate could be used in blowing, but that the fibre products from the latter had less regular morphologies.³³ Again, the drug was amorphously dispersed in the fibres, and the dissolution profiles of the electrospun and electroblown systems were very similar.

6.7 Pressurised gyration

Pressurised gyration can be regarded as a combination of the centrifugal and blowing approaches. First reported by Mahalingam and Edirisinghe in 2013, it involves a pressurised solution of a polymer being rapidly rotated.¹⁶ The experimental set-up is depicted in Figure 6.7. In essence, it comprises a cylinder with a number of small orifices on its surface. This cylinder is loaded with a polymer solution, which is then pressurised by an inert gas (with pressures up to around 0.3 MPa). The cylinder sits inside a static collector and is rotated at speeds of up to 36,000 rpm. The centrifugal forces and pressure drive the polymer solution out through the orifices, and the solvent rapidly evaporates to produce fibres. The technique has the potential to be very easily scalable, with lab set-ups able to produce up to 6 kg of fibres per hour.¹⁶

In the initial development of this technique, the polymer PEO was dissolved in water and a range of processing parameters investigated.¹⁶ Through a judicious choice of polymer concentration, applied pressure and rotation rate, the fibre diameter could be varied between around 60 and 1000 nm. The technique has since been extended to a range of polymers,³⁴ including PVP³⁵ and blends of carboxymethylcellulose, sodium alginate or polyacrylic acid with PEO.³⁶ The latter were found to have significant potential as vaginal mucoadhesive formulations.

Pressurised gyration can also be employed to yield drug-loaded fibres.³⁷ A detailed study of PVP/ibuprofen fibres prepared in this way was performed by Raimi-Abraham *et al.* in 2015.³⁷ Pure PVP fibres from pressurised hydration had nanoscale diameters, but after inclusion of ibuprofen the fibres were found to become wider, with diameters on the micron scale. Scanning electron microscopy images of the fibres

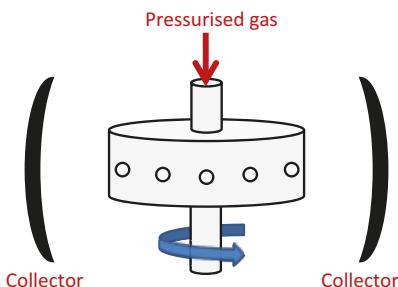


Figure 6.7 A schematic illustration of the experimental apparatus used for centrifugal spinning.

are depicted in **Figure 6.8(a) and (b)**. They comprised amorphous composites of the drug and polymer, and accelerated the dissolution rate of the drug (**Figure 6.8(c)**). In non-sink conditions, super-saturation could be achieved (**Figure 6.8(d)**).

Protein active ingredients may also be formulated into fibres using the pressurised gyration route, as has been demonstrated for the gold-binding dodecapeptide Au-BP2.³⁸ This confirms that the approach is not simply confined to polymers and small molecules, and that complex biomolecules with fragile 3D structures can also be processed.

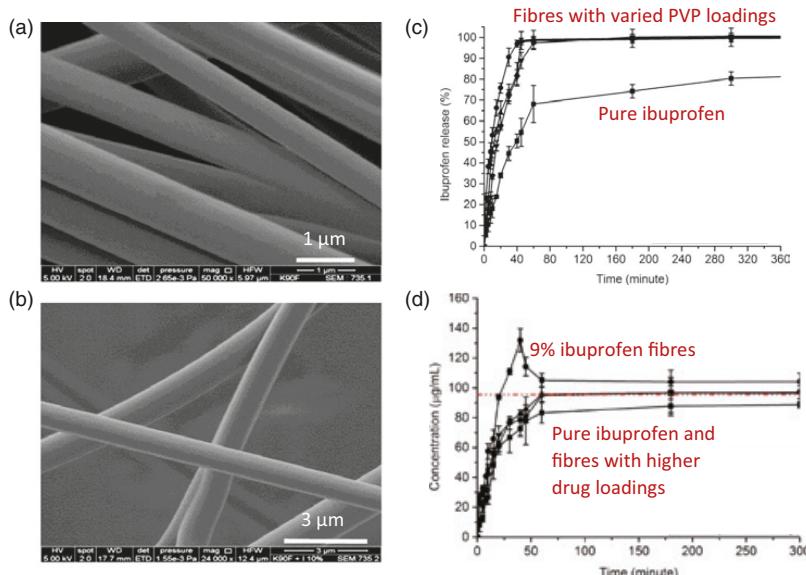


Figure 6.8 Poly(vinyl pyrrolidone) (PVP)-ibuprofen fibres prepared by pressurised gyration. Scanning electron microscopy images of (a) pure PVP fibres and (b) PVP-ibuprofen fibres with a drug loading of 9% w/w, together with drug release profiles under (c) sink and (d) non-sink conditions. In (d), the red line denotes the saturation solubility for ibuprofen, and it is clear that the 9% (w/w) ibuprofen fibres lead to concentrations higher than this in the early stages of the release experiment. (Adapted with permission from Raimi-Abraham, B. T.; Mahalingam, S.; Davies, P. J.; Edirisinghe, M.; Craig, D. Q. ‘Development and characterization of amorphous nanofiber drug dispersions prepared using pressurized gyration.’ *Mol. Pharm.* 12 (2015): 3851–3861. Copyright American Chemical Society 2015. This is an open access article published under a Creative Commons Attribution (CC-BY) License.)

Protein-loaded fibres generated by pressurised gyration have been proposed to have applications in biomineratisation.³⁹ Fibres have also been prepared incorporating metal nanoparticles, with the aim of producing antibacterial formulations.⁴⁰ Most pressurised gyration work has been performed using polymer solutions, but recently it has been shown that the technique can similarly be applied to polymer melts.⁴¹ In the latter study, PCL fibres were prepared loaded with silver nanoparticles, and demonstrated to have antibacterial activity.

6.8 Electrospraying

It would be remiss not to mention the process of electrospraying in the context of this volume. Electrospraying is analogous to the electrospinning process, and uses the same equipment. Rather than producing fibres, however, it yields nano- to micron-sized particles. This is because, rather than ejecting a jet of polymer, the Taylor cone instead emits small droplets in electrospraying (see Chapter 2). As these travel towards the collector the solvent evaporates under the electrical field.

Electrospraying arises when, for instance, the polymer molecular weight is too low and/or the solution too dilute to provide a sufficiently large number of polymer chain entanglements to produce fibres (Figure 6.9). Other than their morphology, the particles from electrospraying are rather similar to the fibres produced in electrospinning. They commonly comprise amorphous solid dispersions, and if made of a fast-dissolving polymer this leads to concomitant enhancement of dissolution rate and solubility. Core/shell and multilayered particles can be prepared by using coaxial and multi-axial spinnerets,⁴² as can Janus particles.

As mentioned in section 4.10, there are relatively few reports on parameter optimisation for multi-axial electrospinning. However, there are several informative studies mapping the material and processing parameters for coaxial and multi-axial electrospraying.⁴³ Given the fact that electrospraying and electrospinning are analogous technologies, the reader may find these reports insightful for guiding material and processing parameter optimisation during multi-axial electrospinning.

An elaborate discussion of the benefits of electrosprayed particles lies outside the scope of this work, and the reader is directed to some recent review articles which discuss these in detail.^{44, 45} In general, however, the sprayed particles can deliver the same functional performance as electrospun fibres. There are some caveats though, and

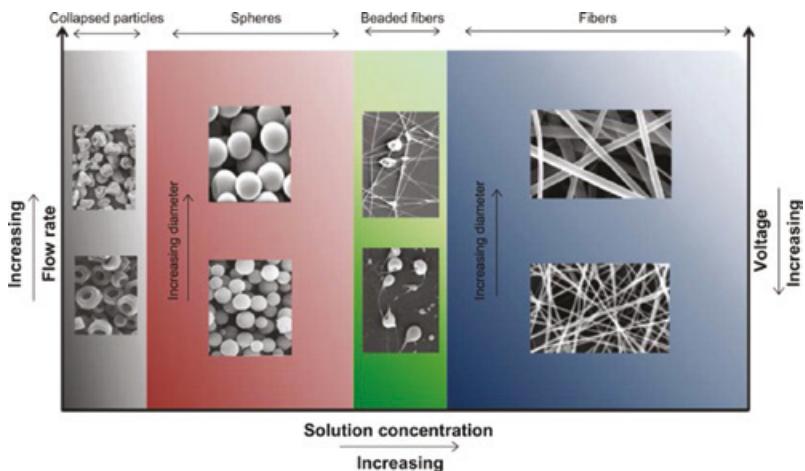


Figure 6.9 A schematic showing the effects of the processing parameters in electrospinning/spraying on the morphology of the products produced. (Reproduced with permission from Zamani, M.; Prabhakaran, M. P.; Ramakrishna, S. 'Advances in drug delivery via electrospun and electrosprayed nanomaterials.' *Int. J. Nanomedicine* 8 (2013): 2997–3017. This is an open access article published under a Creative Commons Attribution (CC-BY-NC) License.)

in particular it can be very difficult to recover the particles if collecting them on a standard metal collector. A mat of electrospun fibres is similar to a bowl of spaghetti, in that while the fibres are not covalently linked together they are intertwined and hard to separate. This makes it simple to peel the mat away from the collector. In contrast, no such entanglement exists with electrosprayed particles, and it is common to suffer poor yields as the particles produced adhere strongly to the collector.

Finally, we should note that a number of researchers have explored the combination of electrospinning and electrospraying. The basic idea is to use the fibre mat from electrospinning as a scaffold to provide certain mechanical or physical properties, for instance on which to grow cells or for tissue engineering, and to load this with electrosprayed particles containing a functional component. This can be undertaken either sequentially (spin the scaffold, and then spray particles on to it) or simultaneously (electrospin and spray at the same time). There are a number of examples of both approaches in the literature.

The first report of the combined technique came from Wang *et al.*, who produced a construct for soft-tissue regeneration by simultaneously electrospinning poly(urethane-urea) fibres and spraying core/shell poly(lactic-co-glycolic acid) (PLGA) particles loaded with the growth factor IFG-1.⁴⁶ The release rate of the growth factor could be controlled by varying the PLGA concentration and molecular weight, and the composite scaffolds appeared to have good biocompatibility and to be able to promote cell growth.⁴⁶

In another example, a recent study by Zhang's team prepared a scaffold of PCL fibres by electrospinning, and then electrosprayed on to this core/shell PLGA particles containing the protein bovine serum albumin.⁴⁷ The resulting composite was found to accelerate the growth of cells, and proposed to have potential in neural regeneration.

Jaworek *et al.* have compared the sequential and simultaneous approaches to assess their efficacy in the coating of Al₂O₃, MgO or TiO₂ nanoparticles on to poly(vinyl chloride), polysulfone or nylon fibres.⁴⁸ The simultaneous process was found to lead to a lower-density particle coating, but also a uniform distribution. The sequential approach gave denser layers of particles, but they were localised in the area of the fibre mat which was directly under the needle used for spraying. Thus, in order to ensure even coverage it was necessary to translate the needle or the fibre mat during the collection process.

In another example, Birajdar and Lee have produced fibres which released the embedded drug upon exposure to sonication.⁴⁹ To do this, they combined electrospinning and electrospraying to produce core/shell poly(L-lactic acid)/PEO fibres with silica nanoparticles embedded in the shell. This process is illustrated in Figure 6.10(a). Different dyes were incorporated in the two compartments of the fibres to aid visualisation. Immediately after electrospinning, the nanoparticles were loosely attached to the surface of the fibres by weak electrostatic forces, but upon annealing the particles became embedded in the fibres (Figure 6.10(b) and (c)). It was found that the release of rhodamine B from the annealed fibres was much more rapid when sonication was applied (Figure 6.10(d)), thus demonstrating that these materials could be used for drug delivery triggered by sound energy.

The combination of electrospinning and spraying has only recently begun to be explored, and much work remains to be done to understand fully the benefits it can deliver. Two recent review articles discuss the concept in detail, and the interested reader is directed to these for more information.^{45d, 50}

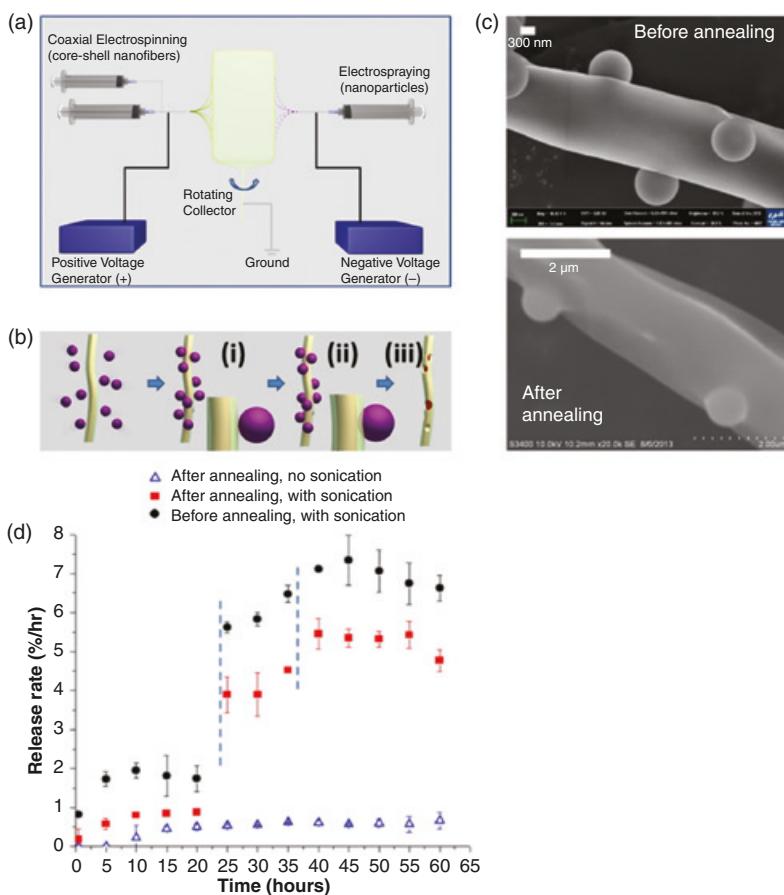


Figure 6.10 Core/shell fibres for sonication-triggered release.

(a) The experimental apparatus used to prepare poly(L-lactic acid)/poly(ethylene oxide) fibres with SiO₂ particles on the surface. In essence, this involves the simultaneous electrospinning of the fibres and electrospraying of SiO₂ particles onto the same collector. (b) A schematic showing the release mechanism. (i) Immediately after electrospinning the particles are located on the surface of the fibres, but (ii) solvent vapour annealing causes them to become embedded (bottom). (iii) Sonication frees the embedded particles, exposing pores in the fibre surface through which the drug can escape into solution. (c) Scanning electron microscopy images demonstrating that annealing causes the particles to become embedded in the fibres. (d) Release data for the model drug rhodamine B, located only in the core of the fibres. It is clear that release is markedly faster after bursts of sonication, as denoted by the dashed blue lines. (Reproduced with permission from Birajdar, M. S.; Lee, J. ‘Sonication-triggered zero-order release by uncorking core–shell nanofibers.’ *Chem. Eng. J.* 288 (2016): 1–8. Copyright Elsevier 2016.)

6.9 Microfluidic spinning

Microfluidic spinning is based on the use of micro (sub-millimetre) channels. A large number of these are located in a single microfluidic chip, and the rate and time of liquid expulsion from each channel are precisely controlled by computer. Microfluidic spinning can be coupled with electrospinning, as described in detail in a recent review by Cheng *et al.*⁵¹ While the productivity of microfluidic methods is a major challenge in scale-up, the technique offers the ability to generate fibres with a high level of complexity not easily achievable by electrospinning. For example, using a digitally programmed microfluidic flow, Kang *et al.* created functional microfibres with continuous spatiotemporal coding along the length of the fibre.⁵² The fibres contained varied chemical compositions and topography, and localised bioactive agents.

Microfluidic spinning therefore has the potential to enable very precisely tuneable loading of different drugs into a single fibre, allowing for programmable release in different parts of the body at different times. The technique is beginning to be explored for drug delivery applications. However, the materials used in microfluidics are usually hydrogels (crosslinked polymer networks solvated with water). These often have fast degradation rates and as a result can be unsuitable for the extended release of drugs, particularly small molecules. To help mitigate this problem, Chae *et al.* developed a microfluidic spinning method using an isopropyl alcohol sheath flow with an aqueous alginate core flow.⁵³ This innovation resulted in nanofibres made of highly ordered alginate molecules. Ahn *et al.* loaded ampicillin into alginate fibres prepared in this manner,⁵⁴ and found that the ordered structure delayed fibre degradation, allowing extended-release profile of ampicillin over 7 days.

6.10 Fibre production on the move

Researchers have expended significant effort to miniaturise nanofibre production equipment in order to make it portable. Edirisinghe's group were the first to develop a handheld electrohydrodynamic 'gun', which can be used to produce wound dressings or tissue scaffolds at the site of need.⁵⁵ This portable apparatus can be used for both electrospinning and electrospraying, as well as coaxial and multi-axial processes. Jiang *et al.* reported a handheld electroblowing device which could precisely deposit fibres on to wound sites,³¹ and as a result achieved rapid cessation of bleeding during liver resection *in vivo*. More recently, a series of

battery-operated or self-powered portable sets of electrospinning apparatus have been developed for both solution and melt spinning.⁵⁶

These portable production approaches enable a non-contact application of drug-loaded nanofibres to a patient, thereby minimising the need for manual contact with both the medicine and the treatment site. Such an approach has the potential to help preserve drug integrity, reduce the risk of wound infection and facilitate timely delivery of sophisticated nanofibre-based treatments, since the need to package and transport the product is eliminated. Mouthuy *et al.* analysed the performance of portable electrospinning using a wide range of commonly electrospun materials, and demonstrated that the portable approach can deliver fibre mats of quality comparable to those produced with larger benchtop set-ups.⁵⁷ Haik *et al.* explored the use of a portable electrospinning device in wound care, and compared the electrospun dressing with traditional paraffin tulle gras dressings on partial-thickness wounds in pigs.⁵⁸ They found no delayed wound healing or signs of infection with either dressing type. The portable apparatus was easy to operate, and could be used to apply different formulations and customisable materials.

6.11 Other techniques

Recently, authors have also begun to explore approaches in which polymerisation and fibre production occur in a single step, preparing a solvent-free mixture of monomers and then expelling these from a spinneret while exposing the jet to, for instance, heat or ultraviolet light to initiate polymerisation.⁵⁹ Supercritical CO₂ has also been explored as an alternative to traditional liquid solvents.⁶⁰ These techniques have been shown to yield fibres, but have not yet been explored for drug delivery purposes. Their feasibility in this regard is thus not established, but the use of supercritical CO₂ requires the use of high pressures and makes the experimental apparatus required more complex and expensive. *In situ* polymerisation could be more promising, but there is a risk of degradation of the active pharmaceutical ingredient during the process (either through chemical reaction with the monomers, or the heat or ultraviolet light used for polymerisation) which would need to be considered.

Another new technique which has been reported very recently is that of pull spinning.⁶¹ This uses a rotating disc with bristles at its surface, which is fed polymer solution from a syringe. The disc spins very quickly, and as a result a solution jet is formed; this ultimately leads to nanoscale fibres. Pull spinning has yet to be applied to drug delivery but would appear to have significant potential in this area.

Table 6.1 The advantages and disadvantages of the major fibre production approaches considered in this chapter

Technique	Advantages	Disadvantages
Direct current (DC) electro-spinning	<ul style="list-style-type: none"> Simple and cheap to set up No use of heat Wide range of literature to build on Many different types of drug delivery system can be produced Can easily be used to make complex architectures Can process a wide variety of fragile active ingredients, including proteins and cells A relatively wide variety of solvents and polymers can be processed Wide range of collector types can be used to align fibres or produce different-shaped scaffolds 	<ul style="list-style-type: none"> Low-throughput batch process – only a few 100 mg of samples per hour can be produced Reproducibly controlling environmental parameters can be difficult, leading to batch-to-batch variation Uses volatile solvents with potential health and safety/environmental implications
Alternating current electro-spinning	<ul style="list-style-type: none"> Relatively simple and cheap to establish No use of heat Relatively high throughput (<i>ca.</i> eight times greater than DC spinning) Drug delivery performance on a par with products from DC electrospinning 	<ul style="list-style-type: none"> Fibre morphology can be less regular than from DC spinning A reduced range of polymers can be processed Little technological development has been undertaken, making new processes harder to establish Uses volatile solvents with potential health and safety/environmental implications
Melt electro-spinning	<ul style="list-style-type: none"> No solvents are used – potentially a greener process than solvent spinning Drug delivery performance on a par with products from DC electrospinning Can offer improved drug delivery performance over solution-spun fibres 	<ul style="list-style-type: none"> Use of heat may cause degradation of labile active ingredients or polymers Apparatus more complex than in solution spinning Fibres have larger diameters than those from solution spinning Little technological development has been undertaken, making new processes harder to establish

Centrifugal spinning	<p>Simple and cheap to set up</p> <p>Can avoid the use of heat/solvent as required</p> <p>Drug delivery performance appears promising</p> <p>Potentially larger-scale than solution electrospinning</p>	<p>Fibres have larger diameters than those from solution spinning</p> <p>Little technological development has been undertaken, making new processes harder to establish</p> <p>Use of one of heat or a volatile solvent is required, which may be problematic for labile drugs (heat) or have safety/environmental problems (solvent)</p>
Blowing	<p>Simple and cheap to set up</p> <p>Can avoid the use of heat/solvent as required</p> <p>Fibre morphology/uniformity can be as good as or better than from electrospinning</p> <p>Drug delivery performance similar to fibres from solution electrospinning</p> <p>Potentially larger-scale than solution electrospinning</p> <p>Can process cells and other fragile active ingredients in the solution-blown process</p>	<p>Little technological development has been undertaken, making new processes harder to establish</p> <p>Use of one of heat or a volatile solvent is required, which may be problematic for labile drugs (heat) or have safety/environmental problems (solvent)</p>
Electroblowing	<p>Can overcome problems with needle clogging experienced in solution electrospinning</p> <p>Higher throughput than standard DC solution electrospinning</p> <p>Drug release behaviour very similar to solution electrospinning</p>	<p>Experimental apparatus somewhat more complex than the separate electrospinning or blowing processes</p> <p>Little technological development has been undertaken, making new processes harder to establish</p> <p>Fibre morphology less uniform than from solution electrospinning</p> <p>Uses volatile solvents with potential health and safety/environmental implications</p>
Pressurised gyration	<p>Experimental apparatus is relatively simple and easily scalable</p> <p>Fibre diameter can be tuned over a wide range</p> <p>Drug delivery properties are promising, and on a par with those of electrospun fibres</p> <p>Can process fragile active ingredients such as proteins</p>	<p>Relatively little technological development has been undertaken, making new processes harder to establish</p> <p>Fibres possibly wider than those produced by electrospinning</p> <p>Generally uses volatile solvents with potential health and safety/environmental implications</p>

6.12 Conclusions

This chapter has presented a brief overview of the alternative approaches to standard solution electrospinning which can be used to generate drug-loaded fibres. A summary of the advantages and disadvantages of each is given in [Table 6.1](#). Some of the techniques discussed involve the use of heat, which can be problematic with thermally labile active ingredients such as proteins or low-melting-point drugs. However, melt approaches are attractive because they obviate the need for volatile (and thus dangerous) solvents, and the use of plasticisers can reduce the temperatures required for processing. Several of the methods discussed are able to operate continuously and produce larger amounts of fibres than standard lab solution DC electrospinning – for instance, AC spinning and pressurised gyration. They are thus possibly more attractive for industry, since they facilitate scaling up. However, the vast majority of the research undertaken on drug-loaded nanofibres to date has used solution spinning with a DC current, and there are already on the market a number of options for scaling up this process. We will consider these in [Chapter 7](#).

6.13 References

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