Chapter Title: Electrospinning fundamentals

2
Electrospinning fundamentals

2.1 Background

Electrospinning applies a strong electric field (kV range) to disperse liquids into fine jets. For the purposes of this volume, these liquids will comprise polymer solutions, emulsions, suspensions or polymer melts containing one or more active ingredients. Electrospinning, together with electrospraying, are sister electrohydrodynamic (EHD) processes, and both involve charged liquid jets. Depending on the properties of the liquid being handled, the application of electrical energy may yield either fibres (electrospinning) or particles (electrospraying or EHD atomisation). This volume focuses on fibres, and thus most attention will be paid to the former. The difference between the two EHD processes will be discussed in more detail in subsequent sections.

Electrospinning at the laboratory scale is a low-cost route to manufacture near-monodisperse micro-/nanofibres with a high surface-area-to-volume ratio and highly tuneable properties. This lends them to a wealth of applications, including biomedical and healthcare products, photovoltaics and photocatalytic materials, stimuli-responsive and smart robotics, optical and chemical sensors and antimicrobial filters, to list but a few.[1] As a result electrospun fibres have been explored in a broad gamut of research areas – for instance, materials science, life sciences and clinical medicine. Electrospinning is highly versatile and can generate uniform fibres with a large range of diameters. The smallest nanofibres have cross-sections containing fewer than 10 elongated molecules, and the largest diameters can be of hundreds of microns, similar to conventional textile fibres. The porosity of the fibre

mat may also be varied over a wide range through systematic changes to the experimental protocol.

In this chapter, we will discuss the key scientific concepts which underpin the electrospinning process, together with the different types of experiment that can be performed and the range of fibres that are produced.

2.2 A brief history of electrospinning

It is only in the last decade or so that researchers have begun to explore the use of electrospun nanofibres in drug delivery, but the EHD process has been studied for centuries. The physical phenomenon underpinning electrospinning was first noted in 1600 by William Gilbert, who described magnetic and electrostatic phenomena in which a droplet could be deformed into a cone shape and a spray of liquid jetted from the droplet when a piece of charged amber was placed close to it. The electric field exerted by the charged amber induced electrostatic charges on the surface of the liquid droplet. When the built-up surface charges overcame the surface tension of the liquid, an aerosol of charged droplets was produced.

Similar observations were made in 1744, when George Mathias Bose reported aerosols produced by applying high electric potentials to liquid droplets at the end of a glass capillary tube. A quantitative explanation emerged towards the end of the nineteenth century: in a series of essays published in 1879 and 1882, Lord Rayleigh calculated the maximum charge that a liquid droplet could carry and remain stable, known as the Rayleigh limit.

Cooley was the first to patent an electrospinning set-up in 1900.[2] This involved the use of auxiliary electrodes to direct fibre deposition on to a continuously rotating reel, similar to the spinning drum in conventional fibre production. Several others have since investigated the phenomenon: in particular, Zeleny's work in 1914–1917 initiated efforts in academia to model mathematically and understand the physics of the EHD process.[3] In the 1930s and 1940s, Formhals registered 11 patents on the process of electrospinning. Many of Formhals' designs laid the foundations for some of the most important contemporary electrospinning set-ups such as needleless spinning,[4] multiple needle set-ups[5] and using parallel electrodes to produce aligned fibres. At the same time, in Russia electrospun fibres were developed into filter materials known as Petryanov filters by Rozenblum and Petryanov-Sokolov. By 1939, the Soviets had commercialised the technology to manufacture

electrospun smoke filter elements for gas masks, which found use during the Chernobyl disaster.[6]

Taylor's work during the 1960s provided a mathematical model for the conical shape of the droplet under the influence of an electric field and experimentally confirmed the Rayleigh limit. Taylor's work further underpinned the theoretical understanding of electrospinning, and the conical shape formed at the spinneret during a stable EHD process is often called the Taylor cone.[7]

Furthermore, Simons filed a patent in 1966 describing non-woven patterned fibrous mats collected on metal grids, electrospun from thermoplastics such as polycarbonate and polyurethane.[8] Simons identified key liquid parameters that must be controlled for electrospinning, including solvent properties such as volatility, viscosity, dielectric constant and conductivity. He particularly highlighted the importance of solution viscosity in obtaining continuous fibres.

In addition to solutions, Larrondo and Manley investigated polymer melts as materials for electrospinning. Melt electrospinning is a valuable approach when the polymer, such as many thermoplastics, does not dissolve in common solvents. However, melt spinning is difficult to set up due to the need to maintain a high temperature in the range of 200°C, and the requirement of a higher voltage (above 25 kV) compared to solution electrospinning (below 25 kV in most cases).[9]

Although the aforementioned studies laid the foundation for the electrospinning technique, it was not until the 1990s, with interest in nanoscience and nanotechnology increasing rapidly, that the EHD phenomena enjoyed resurgent attention from researchers, and the name 'electrostatic spinning' gave rise to the now widely used name 'electrospinning'.[10] During this time, work was focused on furthering understanding of the interrelated electrospinning parameters, electrostatics and fluid dynamics under a strong electric field.[11] Since then, the number of publications on electrospinning has seen an exponential increase year on year.

2.3 EHD fundamentals

Electrospinning can be used to process a very wide range of materials, from liquids such as melts to solutions or suspensions of small molecules, biological materials, cells, bacteria and polymers (both natural and synthetic).[12] Here, we are most interested in the electrospinning of polymers, and thus our discussion will centre on the processing of polymers and
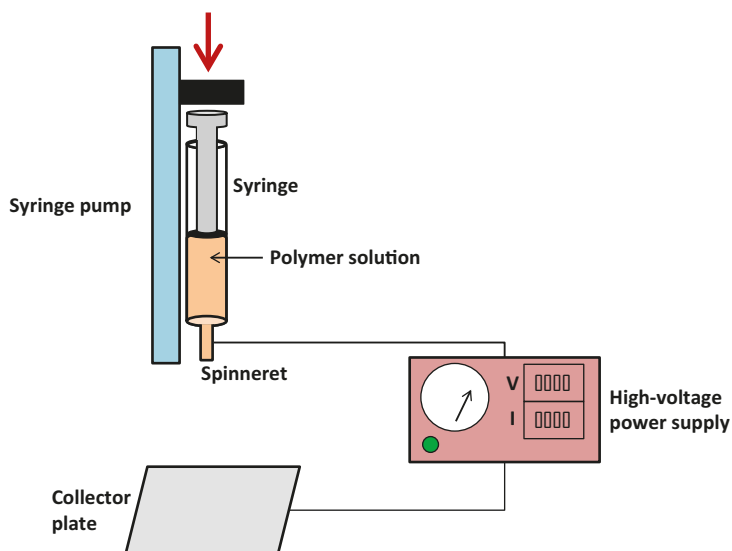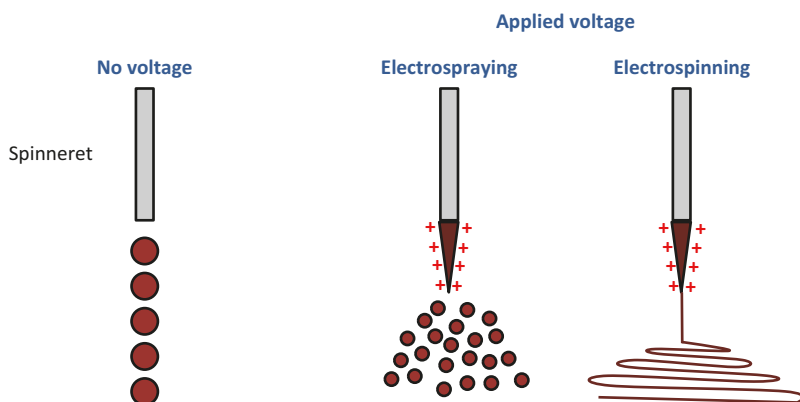
Figure 2.1 A schematic illustration of the apparatus required for electrohydrodynamic experiments.

polymer/drug mixtures. Since the solution approach is more common, the topics will be discussed from this perspective; analogous considerations apply to the processing of emulsions or suspensions.

As explained earlier, electrospinning and electrospraying are 'sister' EHD technologies for the production of polymer-based micro- and nanomaterials. The two are governed by identical theoretical principles and use the same basic equipment. The experimental set-up is illustrated in Figure 2.1.

There are four common components to the basic EHD apparatus: a high-voltage power supply, a precision syringe pump, a syringe fitted with a metal needle (the *spinneret*) and a collector. The power supply is connected to both the spinneret and the collector, with the former usually supplied with either a positive or a negative charge and the latter either grounded or having the opposite polarity to the spinneret. The syringe is filled with a spinnable liquid (e.g. a solution of a polymer, usually with a functional component such as a drug), often referred to as the *working solution*. The solution is extruded through the spinneret at a constant flow rate, controlled by the syringe pump. In conventional electrospinning using a benchtop set-up (described above), a voltage of 5–25 kV is usually applied to the spinneret with a distance of 5–25 cm between the spinneret and the collector. It is worth noting here that, over

Figure 2.2 A schematic illustration of the formation of the Taylor cone.

the last decade, numerous modifications to the electrospinning apparatus have been reported, allowing direct writing/printing of fibres in precise arrangements. One of the commonly studied variations, near-field electrospinning, can now deposit nanofibres with great precision under a voltage as low as 200 V over a distance of 0.5 mm.[13]

If a solution is dispensed from a capillary with no voltage applied, it will exit in the form of spherical droplets, in order to minimise surface tension (an attractive force which acts to minimise surface area). In electrospinning, when a charge is applied to the spinneret, the solution inside acquires a charge, the magnitude of which is dependent on the applied charge, and the solution conductivity and dielectric constant. Repulsive forces between the charges at the droplet surface and the strong potential difference between the charged solution and the collector cause its spherical shape to deform into a cone shape (the *Taylor cone*; Figures 2.2 and 2.3). In electrospinning, at the tip of the cone the polymer solution emits a jet, which rapidly elongates and reduces in diameter. The jet travels away from the spinneret, with the solvent evaporating as the charged solution moves towards the collector. When the jet reaches the grounded collector it discharges. Typically, by this time the solvent has been exhausted, and thus solid products are obtained. As mentioned in section 2.2, electrospinning is strongly dependent on the physical properties of the polymer solution as well as the processing parameters employed.[14] These will be discussed in more detail in sections 2.4 and 2.5.

When the Taylor cone emits a polymer jet, electrospinning occurs to yield fibre products. However, it is also possible that the cone breaks up into droplets: this is electrospraying (Figure 2.2). Similarly to the
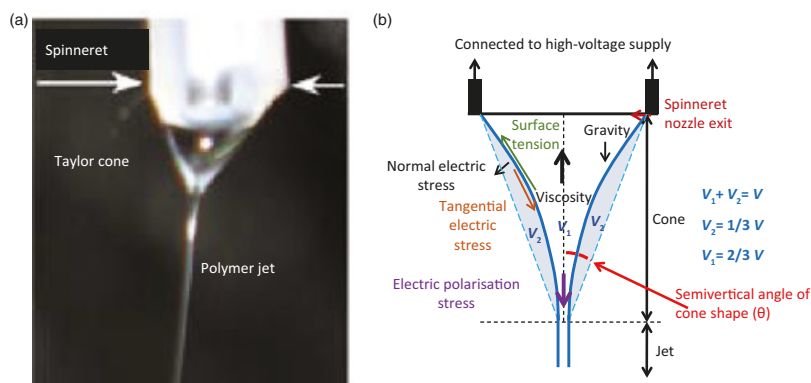
Figure 2.3 (a) A digital photograph of the Taylor cone and ejected polymer jet observed in a typical electrospinning experiment. (Modified with permission from Yu, D.-G.; Williams, G. R.; Gao, L.-D.; Bligh, S. W. A.; Yang, J.-H.; Wang, X. 'Coaxial electrospinning with sodium dodecylbenzene sulfonate solution for high quality polyacrylonitrile nanofibers.' *Colloids Surf. A* 396 (2012): 161–168. Copyright Elsevier 2012.) (b) A geometric diagram of a symmetric liquid cone with a thin jet at its apex, depicting forces acting on the cone jet. *V* is the volume of the conical frustum (i.e. the shape left when the top part of the cone has been cut off), V_1 is the jet volume and V_2 is the space the jet is not occupying in the conical frustum.

electrospinning process, the droplets lose solvent and shrink as they move towards the collector, typically being deposited on it as spherical particles. The explanation for the difference between spinning and spraying lies in the solution properties and processing parameters.

For both electrospinning and spraying, most reports in the literature apply a positive potential at the spinneret. However, it should be noted that the voltage is not constrained to positive polarity, although negative polarity has been reported to produce fibres with larger average diameter.[15]

2.4 Understanding the electrospinning process

Electrospinning involves a range of interlinked parameters broadly categorised into material (here we focus on solution) parameters and processing parameters. Electrospinning is in many ways similar to conventional fibre spinning in textile production. The jet initiated during fibre spinning is generally subjected to tensile, rheological, gravitational, inertial and aerodynamic forces. The difference between electrospinning

and conventional textile spinning lies in the origin of the tensile force initiating the fibre jet. In electrospinning, free charges carried by the liquid interact with the applied electric field and the tensile force inducing fibre jetting is due to the potential difference between the charged liquid in a spinneret and a grounded collector. On the other hand, conventional industrial fibre processing employs mechanical means (spindles and reels) to generate tensile force and initiate fibre formation.

Factors influencing electrospinning include rheology, electrostatics, hydrodynamics and the transport of heat, mass and charge within the polymer jet. For simplicity, electrospinning can be divided into three stages: jet initiation, jet elongation and solidification of the jet to generate fibres. A detailed understanding of the underlying physics is not required for the purposes of this volume, but some insight into the processes underway is useful. For more in-depth discussions, the interested reader is invited to consult recent reviews.[1b, 12, 16]

2.4.1 Jet initiation

The charging of a droplet at the spinneret exit is usually the first step in electrospinning. When a polymer solution is supplied by a syringe pump to the spinneret without an applied voltage, droplets form at the exit and fall off under the influence of gravity. This dripping can continue even with the presence of an applied voltage, and ceases only when the electric field becomes sufficient to balance the surface tension of the liquid.

With the application of voltage, a charge is induced on the surface of the liquid droplet as it exits the spinneret. Repulsions between the like charges in the solution act to oppose the forces of surface tension, causing the droplet to change shape from spherical to conical (Figure 2.3(a)). Taylor supplied a mathematical model for the conical shape of the droplet under the influence of an electric field, showing that a conducting liquid can exist in the form of a cone under the action of an electric field when the semivertical angle θ (Figure 2.3(b)) is approximately 49.3°.[7, 9a] A critical voltage, V_k, is required to transform a spherical droplet to a cone shape at the end of a needle connected to one of the electrodes, and can be predicted based on the semivertical angle using Equation 2.1[7b]:

$$V_k^2 = \frac{4H^2}{L^2}\left(\ln\frac{2L}{R} - 1.5\right)\left((2\cos 49.3°)\pi RT\right)(0.09) \qquad \text{Equation 2.1}$$

In Equation 2.1, H is the spinneret-to-collector distance (in cm), L is the length of the spinneret (cm), R is the inner radius of the spinneret exit

(cm) and T is the surface tension of the fluid (dyn cm^{-1}). All these factors will therefore have an effect on the voltage that needs to be applied to initiate the spinning process. Further, the semivertical angle can also vary with different polymer solutions and melts, and hence the critical voltage required to generate the cone shape droplet varies with different electrospun materials.[17]

Following the establishment of a conical-shaped droplet at the spinneret exit with a sufficiently high applied voltage, additional surface area needs to be created by some means to accommodate the charge build-up on the conical surface. This occurs through the formation of a 'cone jet'. The formation of the Taylor cone and ejection of the jet can be clearly seen by eye in electrospinning experiments (Figure 2.3(a)). A geometric model of a stable cone jet is given in Figure 2.3(b), and illustrates the forces at play during an electrospinning cone jet process.

It is important to be aware of the electric field gradient in the electrospinning experiment. The average gradient (V cm^{-1}) is often described as the potential difference divided by the spinneret-to-collector distance. The resultant value is a good approximation of the field near to the collector. However, the electric field close to the tip of a Taylor cone, just before jet emission, is much higher. After the point of jet emission, the electric field varies across the distance between spinneret and collector in a manner dependent on the surrounding environment. That said, in the interests of establishing functioning experimental parameters, the average field gradient is a sensible parameter to consider when deciding on the voltage and spinneret-to-collector distance being used. In order to operate an efficient and reproducible production process, when varying applied voltage during process optimisation one should keep the collection distance constant to ensure meaningful and systematic optimisation of the field strength.

2.4.2 Electrospinning vs. electrospraying

The distinction between electrospinning and electrospraying depends on the stability of the electrified liquid jet, governed by what is known as Rayleigh instability.[18] The latter depends on the molecular entanglements in the liquid (a frequently used analogy is to imagine polymer chains in a solution as snakes slithering over one another).

There are two key forces acting on the surface of the cone jet, and these oppose one another. Electrostatic repulsion of the charges in the solution promotes an increase in surface area to minimise these repulsions. This drives the charged polymer jet emitted from the Taylor

cone to become longer and narrower. Acting against this, the surface tension seeks to reduce the total surface area of the jet. Which of the two opposing forces prevails depends on the properties of the fluid being processed, particularly its viscosity and surface tension.

Viscosity is a reflection of the degree of molecular entanglement in the liquid,[19] and is fundamental in determining whether a material can be employed to form fibres or not. In electrospraying, the molecular entanglement of the liquid is insufficient to overcome the Rayleigh instability; thus, surface tension prevails and the electrified jet breaks up into small charged particles to minimise surface area.[11a, 20] Electrostatic repulsions between the charged droplets prevent them from coalescing, and as the solvent evaporates the particles shrink. This causes an increasing charge density at their surfaces, and so they break up into even smaller droplets (hence the name EHD atomisation). Electrospraying arises with low-viscosity solutions (i.e. those which flow easily; water has low viscosity, while honey is a high-viscosity fluid). In electrospinning the viscosity of the liquid is high and the molecular entanglements present are sufficient to overcome Rayleigh instability within the charged cone jet. Therefore, instead of capillary break-up the jet takes the form of a fibril undergoing a rapid whipping motion. The jet will elongate and its diameter will decrease until a dried fibre is deposited on the collector.

The molecular weight of the polymer strongly influences the degree of molecular entanglement of the polymer solution, and is thus very important in ensuring electrospinning rather than electrospraying is performed. The explanation for this lies in the manner in which the molecules in a solution interact. Small molecules can easily flow past one another, giving low-viscosity solutions. In contrast, long-chain polymer molecules are able effectively to become wrapped around one another, leading to entanglement. This is illustrated in Figure 2.4.

As a simple analogy, it can be helpful to think about the difference between cooked rice and noodles. Grains of rice are small and exist as discrete units; it is thus very easy to remove a single grain of rice from a bowl. In contrast, noodles are long and narrow, and when placed in a bowl will become wrapped around one another. Extracting a single noodle from the bowl is rather difficult. The same is true for solutions, and a suitable degree of entanglement is critical for successful electrospinning because the tangling of the polymer molecules helps the jet elongation force to outweigh the surface tension. This ensures that the jet continues to the collector to form solid fibres, and does not break down into droplets. Entanglement can be promoted through the use of
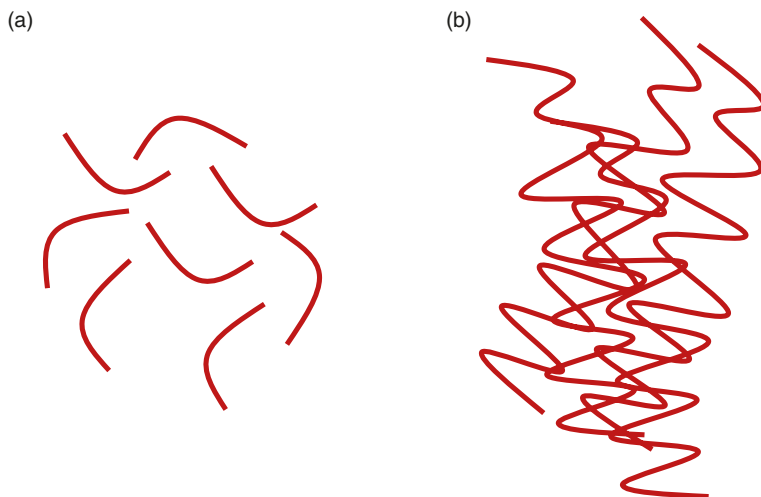
Figure 2.4 The concept of entanglement. (a) Small molecules and low-molecular-weight polymers cannot effectively overlap and entangle. Instead, they flow easily past one another. This leads to low-viscosity solutions which suffer from Rayleigh instability. (b) High-molecular-weight polymers undergo effective entanglement, meaning the force of elongation outweighs the surface tension and permitting electrospinning to be performed.

higher-molecular-weight species and elevated concentrations. However, care must be taken because if the viscosity is too high then spinning will be unstable, resulting in heterogeneous fibre diameters or discontinuous fibres. Moreover, the solvent may deplete quickly at the spinneret exit, leading to blockage.

In addition, it is useful to describe here the 'bead-on-string' or necklace-like morphology of fibres sometimes observed during electrospinning. Bead-on-string arises from a situation intermediate between electrospraying and electrospinning, when charge repulsion and viscous forces are momentarily overcome by the surface tension of the charged liquid. This is often an intermittent occurrence during fibre elongation and considered a defect, resulting in a chain of droplets connected by fibrils. Careful control of the processing parameters during electrospinning can reduce this phenomenon. Methods to avert bead-on-string morphology include moderately increasing the viscosity of the solution either by increasing polymer molecular weight or concentration, or adding surfactants to decrease the surface tension of the solution.

2.4.3 Jet elongation: bending and whipping

As the charged liquid jet travels from the Taylor cone to the collector, it initially follows a linear trajectory (known as the *straight jet*), as it is attracted by the oppositely charged (or grounded) collector. During its journey, it is subjected to a variety of forces with opposing effects. The physical details are out of the scope of this volume and we do not need to consider them in detail here, but the result is that the linear jet does not continue all the way to the collector.[21] Instead, it undergoes what is termed *whipping instability* (also known as bending mode instability or bending instability). This is a rapid elongation process that involves long-waveform perturbations of a liquid column driven by the lateral electric force (Figure 2.3(b)) and aerodynamic interactions, resulting in the jet bending or stretching. This is key in reducing the jet diameter to the nanometre scale to yield nanofibres.

The repulsive Coulombic forces between the charges carried within the polymer solution cause the jet to elongate and narrow continuously until it solidifies. Initially, this results in the emission of a straight jet, but as the jet grows longer the solvent evaporates and the diameter of the jet decreases. The surface charge density of the fibre concomitantly increases, which leads to a further increase in repulsive forces in the jet. Consequently, an increasing amount of time is required to distribute the repulsive charges along the jet length, and therefore it accelerates towards the collector. This produces an extremely high velocity at the leading end of the straight jet. As a result, at a certain point the jet bends and follows spiralling loops (Figure 2.5). Each subsequent loop grows larger in diameter as the jet grows longer and thinner.[1a, 11c] There are repulsions between each segment of the loop, since all parts of the jet bear the same charge, which means the jet follows a bending and whipping pattern before it solidifies on the collector.

The jet may also split into several smaller jets when electrospinning becomes unstable, a phenomenon termed *splaying* or *branching*.[11c] This occurs because of changes in the shape of the jet and/or its charge per unit volume which can arise during the process of jet elongation and loss of solvent. Such changes shift the balance between the repulsive Coulombic forces and surface tension, such that the jet becomes unstable. To reduce the charge per unit surface area, a smaller jet is ejected from the surface of the primary jet. This tends to be seen in highly concentrated and viscous solutions, as well as at very high field strengths.[1a] Splaying should ideally be avoided in the use of electrospinning to produce drug delivery systems, since it leads to inhomogeneities in the products, which can
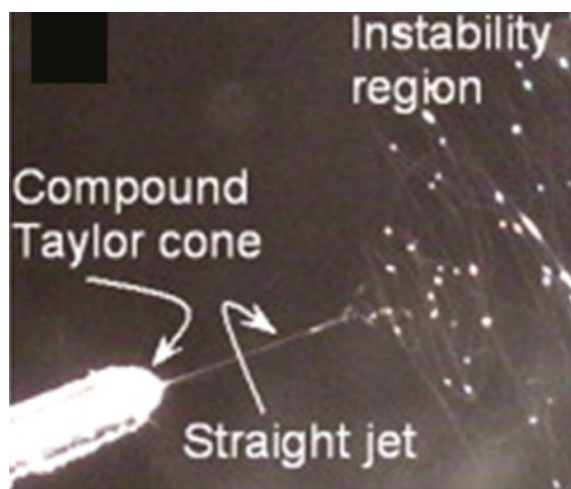
Figure 2.5 A digital photograph depicting bending instabilities during an electrospinning experiment. (Modified with permission from Yu, D. G.; Yu, J. H.; Chen, L.; Williams, G. R.; Wang, X. 'Modified coaxial electrospinning for the preparation of high-quality ketoprofen-loaded cellulose acetate nanofibers.' *Carbohydr. Polym.* 90 (2012): 1016–1023, with permission from Elsevier. Copyright Elsevier 2012.)

preclude the robust and reproducible generation of materials with the desired properties.

2.4.4 Jet solidification

When all the solvent has been exhausted, the jet will become solid. This solidification results in the deposition of dry fibres on the collector.[16] Solvent evaporation begins as soon as the liquid jet is initiated, and increases as the jet undergoes whipping instability. As described in section 1.2, the fibres will collect as a non-woven mesh known as the *fibre mat*. The solidification rate is controlled by the concentration of the solution, the voltage, the spinneret-to-collector distance, the boiling point of the solvent system being used, the environmental temperature and humidity and the surrounding air movement. It is important to balance these to ensure that a dry fibre is produced and the electrospinning process can be undertaken continuously. If solidification happens too quickly (which can occur if the polymer concentration is very high, or the solvent very volatile), then the solution can solidify on the spinneret. This not only results in loss of material but also can block the spinneret.

If the solvent is not all exhausted when the fibres reach the collector then the products are likely to have defects, and not comprise smooth cylindrical fibres. Residual solvent in the fibres may evaporate subsequently, leading to internal voids or porosity being developed and the fibres collapsing in on themselves. This causes their surfaces to wrinkle and/or the fibres to become flattened (Figure 2.6). Alternatively, re-dissolution of the polymer in the solvent may occur, resulting in layers of fibres merging together.
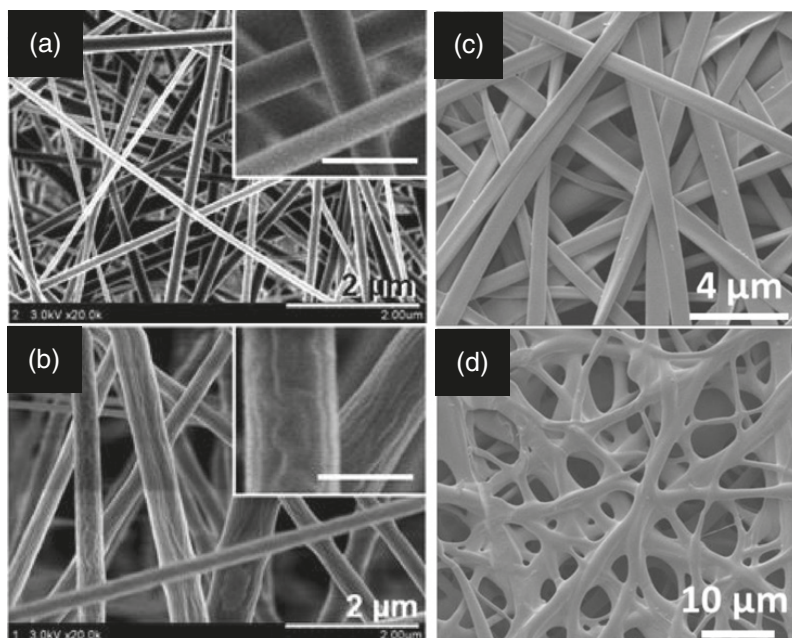
Figure 2.6 Defects that may arise during fibre solidification, showing (a) smooth, cylindrical fibres resulting from a well-optimised process; (b) flattened fibres; (c) wrinkled fibres; and (d) merged fibres. (Images (a) and (b) are modified with permission from Yu, D. G.; Yu, J. H.; Chen, L.; Williams, G. R.; Wang, X. 'Modified coaxial electrospinning for the preparation of high-quality ketoprofen-loaded cellulose acetate nanofibers.' *Carbohydr. Polym.* 90 (2012): 1016–1023, with permission from Elsevier. Copyright Elsevier 2012. Images (c) and (d) are modified with permission from Jia, D.; Gao, Y.; Williams, G. R. 'Core/shell poly(ethylene oxide)/Eudragit fibers for site-specific release.' *Int. J. Pharm.* 523 (2017): 376–385, with permission from Elsevier. Copyright Elsevier 2017.)

During the drying process, *conglutination* can also occur. This is a process by which partially solidified jets come into contact, resulting in fibres that are fused together at these points of contact. The attachments dictate the mechanical properties of the fibre mat, with more contact points making it more rigid.

2.5 The parameters affecting electrospinning

The electrospinning process is affected by many parameters, which can helpfully be divided into solution, processing and environmental parameters. Solution parameters include the polymer molecular weight and structural conformation (these strongly influence the minimum concentration and viscosity required to form continuous fibres) and the choice of solvent or solvent mixtures (which strongly influences surface tension, rate of evaporation, dielectric constant and electrical conductivity). Processing parameters are dependent on the electrospinning apparatus design, but chiefly comprise the applied voltage, spinneret-to-collector distance and the solution flow rate. Each parameter will influence the morphology of the fibres obtained. Through their optimisation and control it is possible to tune the electrospinning process to yield nanofibres with the desired morphology and diameters. In addition, environmental parameters – the humidity, temperature and air circulation speed of the surroundings in which the process takes place – are also important to consider. These are described briefly below, and discussed in more detail in subsequent chapters.

2.5.1 Solution parameters

The fibre formation process relies on the elongational stretching of the polymer solution exiting the spinneret. The dominant influence of the properties of the polymer solution on the electrospinning process and the resultant fibre morphology cannot be overstated. The properties of the polymer solution, such as viscosity, surface tension, conductivity, dielectric constant and volatility, change with the molecular characteristics of the polymer, the concentration of the polymer in solution, and the choice of solvents used. Understanding the polymer solution brings profound insight in achieving a successful electrospinning process.

Key solution parameters which need to be considered are as follows.

Concentration: The concentration of the polymer in solution is a determining factor for the formation as well as diameter and morphology

of the fibres from electrospinning. A critical minimum concentration c_e is needed to allow sufficient molecular chain entanglement to overcome surface tension and prevent the electrospinning jet from breaking up. Concentrations below c_e will produce droplets when electrified (electrospraying). At concentrations above c_e, electrospun fibre diameter increases with increasing polymer concentration and the frequency of bead-on-string defects decreases, eventually leading to the formation of beadless uniform nanofibres. The value of c_e is dependent on the molecular chain length, macromolecular structure and the solvent(s) selected to dissolve the polymer.

Molecular weight and molecular chain length: The polymer molecular weight inversely affects the value of c_e required to enable electrospinning.[22] A polymer molecule generally has a long chain-like geometry, but these chains may be branched and there may be crosslinks between chains. These characteristics depend on the polymer's chemical structure and the synthesis method. A linear polymer with a high molecular weight (above 3000 g mol^{-1}, preferably above 10,000 g mol^{-1}, and more preferably above 50,000 g mol^{-1}) leads to a lower c_e for fibre formation in electrospinning than a branched polymer with low molecular weight when dissolved in the same solvent.

Solution viscosity: Viscosity reflects the degree of polymer molecular chain entanglement in a solution. The solution viscosity is influenced both by the molecular weight of the polymer and the properties of the solvent used. Hence, it can be adjusted by both varying polymer concentration in solution and/or changing the solvent. The minimum solution viscosity required to enable electrospinning is that of a solution with polymer concentration higher than the relevant c_e value.

If the viscosity is very low, then electrospraying will occur and the products will comprise particles. An intermediate viscosity will lead to beaded fibres (a situation intermediate between electrospraying and spinning). The effect of viscosity on fibre morphology is depicted schematically in Figure 2.7.

It might therefore be thought that the higher the viscosity the better, but unfortunately the situation is not that simple. A greater viscosity will make it more difficult for the jet to become elongated and narrow, thus leading to thicker fibres. Helix-shaped fibres have also been observed when working with very-high-viscosity solutions,[23] and incomplete drying of a high-viscosity jet can lead to the formation of flattened ribbon-like fibres.[24] Finally, if the viscosity is too high the polymer solution may solidify on the spinneret, leading to it becoming blocked.
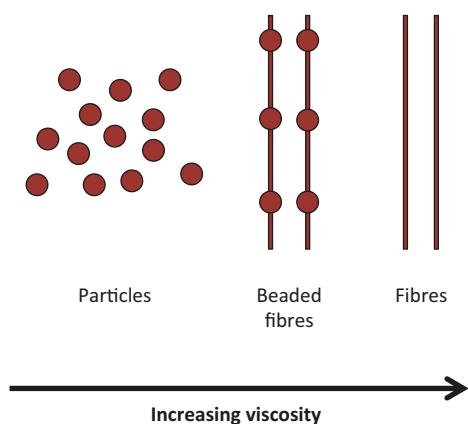
Figure 2.7 The effect of solution viscosity on the products from electrohydrodynamic processing.

The range of viscosities that allows electrospinning is specific to the polymer and solvent system used. For example, Doshi and Reneker found that the optimum viscosity range for electrospinning poly(ethylene oxide) (PEO) nanofibres is 800–4000 mPa s.[21] On the other hand, in a comprehensive investigation on electrospinning poly(acrylonitrile) dissolved in dimethyl formamide (DMF), Baumgarten observed that smooth submicron fibres could be electrospun when the viscosity of the solution was 170–21500 mPa s.[25]

Surface tension: Surface tension acts together with the viscosity of the polymer solution to oppose the electrical drawing force. To begin the electrospinning process, the surface tension must be overcome by the repulsive forces between the charges in the polymer solution. In Equation 2.1, the critical voltage for cone formation V_k is proportional to surface tension T, and thus liquids of higher surface tension require higher V_k for electrostatic processing. However, a higher electric field also means greater potential leakage of the surface charge on the jet into the surrounding air. This makes the cone jet unstable, leading to defects and non-uniformity in the fibres. Defects such as bead-on-string formation can arise when the surface tension of the solution briefly overcomes the elongational forces.

Solutions with very high surface tensions can thus be difficult to spin, as they require significantly stronger electric force to overcome this. In addition, the higher the surface tension, the greater the forces opposing jet elongation, and thus the more likely it is that it will break up into droplets or form bead-on-string defects.

At a fixed polymer concentration, reducing the surface tension has been reported to be an effective route to improve the morphology of the electrospinning product from beaded fibres to smooth fibres.[23] Most solvents used for electrospinning have relatively low to moderate surface tensions (20–45 mN m^{-1} at 20°C), but working with water, a high surface tension solvent (72.75 mN m^{-1} at 20°C) with low volatility (boiling point at 100°C) can be problematic. Surfactants can be added to the working solution to reduce surface tension if required, but these will be carried through into the fibre products, which may be undesirable.

The surface tension of a polymer solution is temperature-dependent, but also varies with the choice of solvent(s), and the concentration and the chemical structure of the polymer. As the electrospinning jet travels towards the collector, solvent evaporation leads to an increasing polymer concentration in the jet. The surface tension of the jet is therefore likely to evolve upon exiting the spinneret and landing on the collector.

Electrical conductivity: The greater the electrical conductivity of the solution, the more easily charge can accumulate in it to build up sufficient tangential stress for fibre elongation, and hence the lower the voltage required to initiate jet electrospinning. Fibres with thinner diameters also result from more conducting solutions. The addition of trace amounts of inorganic salts or ionic organic species to the solution offers a simple route to enhance electrical conductivity, if required. Solutions of zero conductivity cannot be electrospun. However, if the electrical conductivity of the liquid is too high, electrical discharge into the surrounding air will occur, resulting in unstable jetting or halting the electrospinning process altogether. For instance, Morota *et al.* found that increasing the conductivity of aqueous solutions of PEO changed the stable cone jet to an unstable multijet, and solutions with conductivity above 0.5 S m^{-1} could not be electrospun.[26]

Dielectric constant: A temperature-dependent property, the dielectric constant ε (otherwise known as the relative permittivity) of a substance is a measure of the extent to which it concentrates the electrostatic lines of flux when placed in an electric field. It is defined as the ratio of the amount of stored electrical energy when a voltage is applied relative to the permittivity of a vacuum. Solvents of different dielectric constant values interact with the electric field differently during solution electrospinning. Solutions in solvents of an appropriately high range of dielectric constants (ε value above 30 at 20°C) allow a more even distribution of the

surface charge on the jet, and have been reported to be easier to electrospin and to produce fibres with smaller diameters.[27]

Volatility: Solvent evaporation has a significant effect on fibre morphology and diameter. Selecting a relatively volatile solvent allows the fibre to dry completely upon reaching the grounded collector, avoiding defects such as fused wet fibres. However, solvent volatility also affects the kinetics of phase separation and hence the morphology of the electrospun fibres obtained. Highly volatile solvents can cause a hard solidified shell to form on the elongating fibre before complete drying can occur, trapping the solvent inside the fibre. As the residue solvent slowly diffuses out of the fibre shell, defects such as wrinkled or porous surface morphologies can occur. In addition, rapid solvent evaporation from the jet can hinder the production of smaller fibre diameters, since there is less time for elongation before complete solidification occurs. Hence, volatile solvents such as acetone, dichloromethane and chloroform are often reported to generate fibres with a larger average diameter than solvents such as water and DMF (though other solvent properties such as water and DMF having moderately high dielectric constants can also contribute to such observations).

Solvent choice: The choice of solvent or solvent mixture strongly influences the viscosity, surface tension, electrical conductivity, dielectric constant and volatility of the solution, and thus is of crucial importance. The selected solvent must not only provide appropriate electrical conductivity, viscosity and surface tension, but also needs to be able to dissolve/disperse the polymer and the functional component of interest at appropriate concentrations.

In general, it is useful to know that using a solvent of lower solubility for the polymer(s) of interest can enhance nanofibre formation or dramatically change the value of the critical concentration, c_e.[28] For example, Shenoy et al.[22] found that poly(vinylidene fluoride) (PVDF: molecular weight (Mw) 180 kDa) fibres can be electrospun at concentrations as low as 7.5% w/w using acetone, whereas a concentration of 30% w/w PVDF in DMF was necessary for successful electrospinning. In this case, acetone was a marginal solvent for PVDF whereas DMF was a good solvent. The addition of acetone to the PVDF solution in DMF significantly lowered the c_e necessary for fibre formation.

2.5.2 Processing parameters

Process parameters include the operating parameters (such as applied voltage, flow rate, diameter of the spinneret inner orifice and collection

distance), the spinning environment (temperature and humidity) and the set-up design (e.g. the choice of material used as the collection substrate).

Voltage: A sufficient voltage must be applied to initiate jet formation, and as discussed above, this threshold voltage depends mainly on solution properties such as surface tension and viscosity. Increasing the voltage beyond the threshold for jet initiation increases the degree of whipping instability and hence the elongation of the fibre jet. However, on the other hand, it also reduces the flight time between the spinneret and the collector. Hence, its effect on the fibre products is controversial. While numerous studies have observed decreasing fibre diameter with increasing applied voltage,[29] many others have shown minimal effect or an increase in fibre diameter.[30]

This discrepancy in the literature is a result of the interrelationship between applied voltage and other parameters such as flow rate and collection distance. If the voltage is too high and the flow rate is sufficient to maintain an increased rate of mass transfer, then multiple jets may be formed from the Taylor cone. This should be avoided, because it can lead to the products comprising several different subpopulations of polydisperse fibres. Voltage is therefore an important parameter, but no general statements can be made, other than to say it must be greater than V_k, the critical voltage needed to overcome the surface tension and emit a jet, and not so high as to lead to multiple jets forming or deplete the cone-shaped droplet at the nozzle exit.

In the majority of cases, a positive voltage is applied to the spinneret. Electrospinning with a negative voltage is also possible (as indeed is alternating current (AC) electrospinning, where the voltage alternates from positive to negative values), but both are much less explored than the positive polarity set-up. Studies have shown that AC current can cause non-uniform fibre diameters, and a negative polarity at the spinneret can result in fibres with larger average diameters.[15, 31]

Flow rate: Flow rate, also known as infusion rate or feed rate, is the rate at which the polymer solution is pumped into the spinneret to feed the spinning cone jet. The rate at which the solution is ejected from the spinneret collectively depends on the inner size of the spinneret orifice, the applied voltage (which provides the electrical force pulling the solution out of the needle) and the flow rate at which the solution is fed into the needle. As mentioned earlier, the voltage required for jet initiation is in turn dependent on the polymer solution properties. Therefore, at any given voltage, an optimum range

of flow rates exists for a polymer material, which varies with the inner diameter of the needle. Fibre diameter increases and uniformity decreases with flow rates higher than this optimum range; a higher than optimum flow rate may not provide enough time for the polymer solution to become sufficiently charged to generate the Taylor cone, and some droplets may form upon exiting the spinneret.

A faster flow rate will usually lead to thicker fibres at a given voltage, because more mass is dispensed in a given unit of time. It may also produce fibres with defects such as beads or wrinkles if the solvent does not have time to evaporate completely before reaching the collector. Multiple jets can additionally be initiated if the flow rate is too high. On the other hand, at flow rates lower than the optimum range, electrospinning becomes discontinuous as the cone at the tip of the nozzle becomes depleted and even recedes into the needle.

Reducing the flow rate, of course, also has the disadvantage of increasing the time required to produce the desired amount of material. Hence, balancing the flow rate and applied voltage is vital in obtaining and maintaining a stable cone jet during electrospinning. To ensure steady mass transfer and continuous fibre production, the mass of liquid supplied to the needle tip needs to be equivalent to the mass of the jet spinning out of the needle.[32]

Spinneret: Metal spinnerets are most commonly used. In general, these comprise needles with small inner orifice diameters to generate narrow fibres.[33] The single-bore needles used for electrospinning monolithic fibres usually have diameters below 2 mm. A narrower-bore needle can be helpful in reducing the fibre diameter and also in preventing the formation of beaded fibres, but is also more prone to becoming blocked.

Spinneret-to-collector distance: The shorter this distance, the higher the electric field strength will be. However, the flight time will reduce with distance, and short distances can hence lead to incomplete solvent evaporation and the concomitant problems discussed in section 2.4.4. The optimum range for collection distance is most commonly 100–200 mm for conventional set-ups. Special apparatus such as near-field electrospinning, which requires a much lower collection distance, will be discussed in Chapter 6. Longer distances have been reported to lead to narrower fibres, because a greater period of elongation is possible. However, long distances beyond the optimum collection range will cause significant increases in the flight time, which can result in increased corona discharge and Rayleigh instability, leading to large fibre diameters and defects such as fused or beaded fibres.[34] For

example, when increasing the collection distance from 10 to 30 cm, Kidoaki *et al.* (2006) observed a steady increase in fibre diameter from electrospun polyurethane in tetrahydrofuran and DMF mixed solvents.[34]

Finally, it is important to note that the polymer jet will discharge itself at the earliest opportunity, and thus using long distances can result in low yields and thinner fibre mats because the product is deposited over a larger surface of the collector, and in some cases not on the collector at all, but rather on the walls of the electrospinning chamber.

2.5.3 Environmental parameters

Environmental parameters are in essence the temperature and humidity of the location in which electrospinning takes place. It is also worth noting the surrounding speed of air flow: the presence of fast movements or changes in the degree of ventilation in the laboratory could affect the stability of the cone jet and the rate of solvent evaporation, leading to changes in the products obtained. To ensure reproducibility, it is usually best to conduct electrospinning in a space enclosed with an electrically insulating material such as plastic sheets.

An increase in humidity from 20% to 40% can reduce the as-spun fibre diameter, depending on the particular solvent used. This is because the evaporation rate of a solvent from a free surface is proportional to the difference between the vapour pressure of the solvent and the vapour pressure in the surrounding air. Increasing humidity retards the rate of solvent evaporation, thereby allowing longer time for fibre elongation. However, high humidities (> 60%)[35] can be problematic and often result in the formation of a film or poorly defined fused fibres on the collector, particularly with hygroscopic polymers such as poly(vinylpyrroli-done).[35a] This is because the absorption of water is favoured by a higher humidity and the concomitant greater partial pressure of water in the atmosphere; the presence of such high amounts of water in the air excessively retards the rate of solvent evaporation, allowing wet fibres to land on the collector and the possibility for this atmospheric water to interact with the products. If the polymer is insoluble in water it may precipitate in high-humidity environments, which can lead to blocking of the spinneret, thicker fibres, porosity or defects driven by phase separation in the products.

Higher temperatures will generate two opposing effects in electrospinning: on the one hand, it provides more energy to the molecules in solution, thereby increasing the electrical conductivity and reducing viscosity and surface tension of the solution. This facilitates the formation of

finer fibre diameters as well as leading to higher polymer chain alignment (enhancing mechanical properties).[36] However, an increase in temperature also provides additional energy to accelerate the rate of solvent evaporation, reducing the time available for fibre elongation before solidification. Increasing the temperature from the ambient temperature of *ca.* 20°C to 40°C leads to reduced fibre diameter,[35a, 37] indicating that the former effect dominates over this temperature range. Fibre diameter was found to increase at temperatures higher than 40°C, however, indicating that here the faster solvent evaporation factor has overtaken the effect on surface tension and viscosity. There is very limited literature on the effect of temperatures cooler than the ambient temperature of approximately 20°C. However, Vrieze *et al.* observed reduced fibre diameters at 10°C and attributed this to a reduced rate of solvent evaporation.[35a]

2.5.4 Solvent and polymer selection

Pillay *et al.* have published an excellent review including the typical parameter ranges used for the electrospinning of a range of polymers for drug delivery purposes.[38] A summary is given in Tables 2.1 and 2.2.

2.6 The experimental set-up

The equipment needed for electrospinning will be briefly introduced in this section. More detail will be presented in subsequent chapters where the different types of electrospinning are discussed.

2.6.1 Basics

As discussed in section 2.3, the basic electrospinning apparatus consists of a high-voltage power supply, syringe pump, syringe fitted with a spinneret and a collector. All of these can be purchased at relatively low cost, and it is possible to construct a home-made set-up for a few thousand dollars (certainly less than $4000). Alternatively, a range of ready-made commercial apparatus exists, for instance from YFlow,[39] SprayBase,[40] or IME Technologies.[41] These are more expensive, ranging from around $15,000 to more than $100,000, but have advantages in terms of ease of getting the equipment up and running and access to specialist advice, of particular benefit to groups working on electrospinning for the first time.

There are two ways of setting up the orientation between the spinneret and the collector in electrospinning: vertically or horizontally.

Table 2.1 The properties of some solvents commonly used in the preparation of electrospun drug delivery systems

Solvent	Boiling point (°C)	Other properties	Fibre morphology	References
Dichloromethane	39.8	Low dielectric constant, high surface tension	Beaded, large diameter	*J. Biomater. Sci.* 2006, 17, 9, 1039 *J. Polym. Sci. B* 2004, 42, 20, 3721
Chloroform	61.2	High intrinsic viscosity	Beaded at very low polymer concentration, smooth at higher concentration	*Polymer* 2004, 45, 9, 2959
Methanol	64.7	High dielectric constant	Small fibre diameter with dichloromethane/methanol mixtures until the methanol concentration reached 50%, then rising fibre diameter	*J. Biomater. Sci.* 2006, 17, 9, 1039
Tetrahydrofuran	66	High dipole moment, good conductivity	Smooth and beaded, ribbon-like, high pore density	*Polymer* 220, 43, 16, 4403 *Eur. Polym. J.* 2005, 41, 3, 409
Ethyl acetate	77.1	High dielectric constant, fair conductivity	Smooth and beaded, ribbon-like	*Eur. Polym. J.* 2005, 41, 3, 409
Ethanol	78.3	Low surface tension, high intrinsic viscosity	Smooth, large diameter	*Polymer* 1999, 40, 16, 4585 *J. Polym. Sci. B* 2004, 42, 20, 3721 *Polymer* 2004, 45, 9, 2959
Methyl ethyl ketone	79.6	High dipole moment, good conductivity	Flat, ribbon-like, very few beads	*Eur. Polym. J.* 2005, 41, 3, 409

Dichloroethane	83.5	High dipole moment, fair conductivity	Smooth and beaded, C-shaped	*Eur. Polym. J.* 2005, 41, 3, 409
Water	100	Low intrinsic viscosity	Beaded, small diameter	*Polymer* 1999, 40, 16, 4585 *Polymer* 2004, 45, 9, 2959
Dimethyl formamide	153	High dipole moment, high conductivity, low intrinsic viscosity	Smooth and beaded, round	*Polymer* 2004, 45, 9, 2959 *Eur. Polym. J.* 2005, 41, 3, 409

Table 2.2 Polymers and solvent types commonly used in the preparation of electrospun drug delivery systems, together with examples of the drugs which have been incorporated

Polymer	Solvent	Active ingredient(s)	References
Cellulose acetate	2:1 acetone/ dimethylacetamide	Naproxen, indomethacin, ibuprofen, sulindac	*Polymer* 2007, 48, 17, 5030
		Curcumin	*Polymer* 2007, 48, 26, 7546
		Vitamins A and E	*Eur. J. Pharm. Biopharm.* 2007, 67, 2, 387
Poly(ε-caprolactone)	7:3 dichloromethane/ methanol	Heparin	*Biomater.* 2006, 27, 9, 2042
	3:1 chloroform/ethanol	Resveratrol, gentamicin	*J. Biomed. Mater. Res. A* 2006, 77, 1, 169
Poly(ethylene oxide)/poly(ε-caprolactone) blend	Chloroform	Lysozyme	*Colloids Surf. A* 2008, 313–314, 183
Poly(vinyl alcohol)	Deionised water	Ketoprofen	*Mater. Sci. Eng. A* 2007, 459, 1–2, 390
		Sodium salicylate, diclofenac, naproxen, indomethacin	*Nanotechnol.* 2006, 17, 9, 2317
Gelatin/poly(vinyl alcohol) blend	Gelatin in formic acid, poly(vinyl alcohol) in deionised water	Raspberry ketone	*Carbohydrate Polym.* 2007, 69, 3, 538
Poly(lactic-co-glycolic acid)	Dichloromethane/ dimethyl formamide	Paclitaxel	*Biomater.* 2008, 29, 20, 2996
	Dimethyl formamide	Cefoxitin sodium	*J. Control. Release* 2004, 98, 1, 47

| Polyurethane	Dimethyl formamide	Itraconazole	*J. Control. Release* 2003, 92, 3, 349
	Dimethylacetamide	Ketanserin	
Poly(L-lactic acid)	2:1 chloroform/acetone	Doxorubicin HCl	*J. Control. Release* 2005, 105, 1–2, 43
		Tetracycline HCl	*J. Macromol. Sci. B* 2006, 45, 4, 515
	Chloroform	Cytochrome *c*	*J. Control. Release* 2008, 127, 2, 180
	Dichloromethane	Bovine serum albumin	*Biomacromol.* 2006, 7, 8, 2327
Poly(ethylene-co-vinylacetate)	Chloroform	Tetracycline HCl	*J. Control. Release* 2002, 81, 1–2, 57
Poly(ethylene glycol)–poly(L-lactic acid) copolymer	Chloroform	Doxorubicin HCl	*Eur. J. Pharm. Biopharm.* 2008, 70, 1, 165 *J. Control. Release* 2005, 108, 1, 33
Poly(acrylic acid)/ poly(allylamine hydrochloride) blend	Deionised water	Methylene blue	*Colloids Surf. B* 2007, 58, 2, 172

The difference lies simply in the direction of liquid travel: in the former approach, liquid is dispensed in a direction perpendicular to the floor and aided by gravity, while in the latter it travels parallel to it. Both have advantages and disadvantages. In the horizontal approach, the force of gravity on the fluid jet can become significant if the collection distance is greater than 10 cm, and the jet can be dragged downwards, away from the collecting area, as a result. This can cause fibres to build up at the bottom of the collector, or even below it, compromising the effective yield of the process. In the vertical approach, gravity is acting in the same direction as the electrostatic accelerating force. However, the downside of the vertical approach is that, if any droplets are formed during the process (e.g. when pausing or restarting the process), these can potentially fall on to the collector, compromising the quality of the products. In the horizontal approach, the droplets will fall to the bottom of the experimental chamber and will not reach the collector, and thus the product can be of higher quality.

2.6.2 The power supply and syringe pump

These are commercial items which can be purchased from a large number of different suppliers. The major issues to consider when buying are the cost *vs.* the precision and stability of the power supply and pumps, and whether the apparatus meets the user's needs in terms of the range of voltages which the supply will generate and the rates at which the pump will dispense. In general, a simple power supply capable of producing a positive voltage up to 25 kV should suffice (most electrospinning is performed between around 5 and 25 kV).

2.6.3 The spinneret

In the simplest electrospinning experiment, termed *monoaxial* electrospinning, a solution of a polymer and drug is dispensed through a single-bore blunt-end needle, most often made of a conductive and solvent-resistant metal such as stainless steel. This gives a monolithic product, with the drug and polymer typically evenly and homogeneously blended throughout the fibres. However, it is possible to process two, three or even more liquids as compound jets (co-flowing liquid jets) and a range of more complicated spinnerets such as concentric or multi-needle designs can be prepared to generate sophisticated nanostructures made of multiple polymers and/or active pharmaceutical ingredients. A summary of the most important designs is given in Figure 2.8. To process multiple liquids, each is loaded into a separate syringe and dispensed independently using multiple syringe pumps.
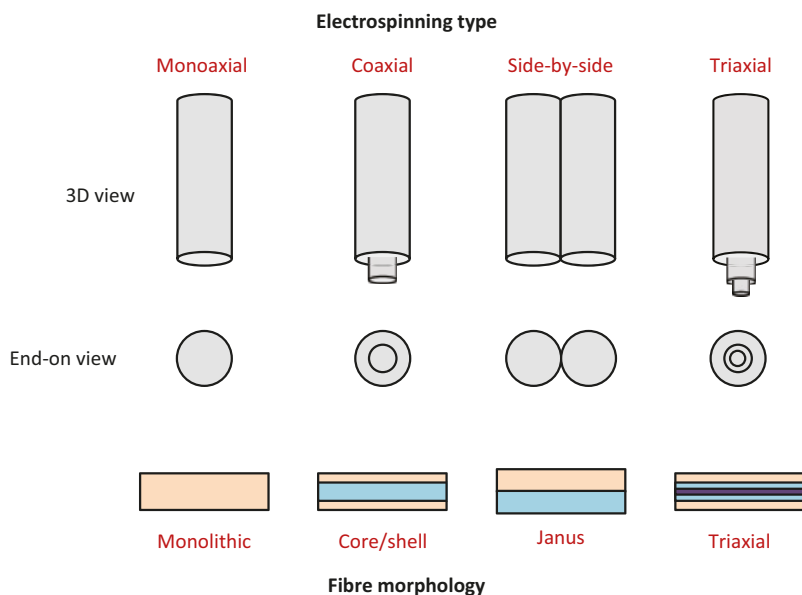
Figure 2.8 Spinneret designs for different types of electrospinning, and the structures of the fibres produced.

Coaxial electrospinning uses a coaxial needle that contains two capillary channels arranged in a concentric manner. Each channel is infused with a polymer solution at an individual flow rate. If the experiment is well designed and optimised there will be minimal blending between the two solutions, and since the electrospinning process is very fast the concentric structure of the spinneret will result in core/shell fibres with two distinct compartments (Figure 2.8). Similarly, if two needles are arranged *side by side* the fibres produced should have a Janus morphology, with two different sides. Moving up to three or four liquids can yield three-layer or even four-layer fibres if a triaxial or quad-axial concentric spinneret is used. There are a range of more complicated spinneret designs but the key types of electrospinning as far as this volume is concerned are monoaxial, coaxial, triaxial/quad-axial, and side-by-side; they will be discussed in more detail in subsequent chapters.

2.6.4 The collector

The speed at which each layer of the produced nanofibres becomes discharged upon reaching the collector plays a significant role in

controlling the spacing and density of the fibre mat. This discharging process is affected by the dielectric properties, surface area and the collective conductivity of the collecting substrate. Various geometries of collectors have been designed to achieve better control of fibre deposition density and alignment. A comprehensive review on collector designs has been undertaken by Teo and Ramakrishna.[42]

The simplest collector is a flat conducting collector plate, usually a metal plate coated in aluminium foil. This will give a mat of non-woven fibres which are randomly oriented. For most drug delivery applications, this is perfectly satisfactory. However, a problem can arise when spinning for long periods of time (> 2 h) to prepare larger amounts of product. As the layer of fibres on the collector builds up and becomes thicker, it acts as an insulating coating to the grounded collector. This reduces the electrical field gradient to new fibres being deposited, which can result in incomplete evaporation of solvent and defects forming at the top of the mat.

It can thus sometimes be useful to employ a rotating mandrel collector. This increases the area of fibres which can be collected, and is depicted in Figure 2.9. Here, the collector comprises a conducting cylinder which rotates along its long axis. To ensure even coverage of the collector, the spinneret is moved back and forth along the length (*rastering*). This generates a tubular structure. At the end of the experiment, a scalpel can be used to cut through and remove the fibres as a flat mat. If the tube can be rolled off the mandrel without damaging it, the rotating mandrel set-up can be used to prepare tubular scaffolds for tissue engineering, for instance of veins or arteries.[43]

With the recent explosion of interest in electrospinning technology, a number of more sophisticated collecting systems have been reported.
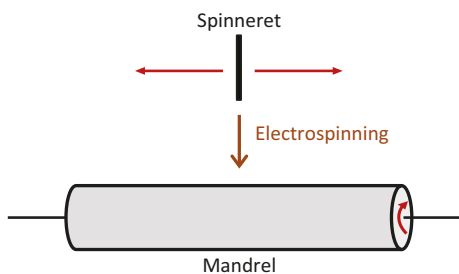
Figure 2.9 A schematic showing the use of a rotating mandrel collector with a rastering spinneret.

For instance, for tissue-engineering scaffolds it can often be desirable to obtain aligned fibres. This can be achieved by rotating a cylindrical mandrel very quickly (at a rate of hundreds or thousands of revolutions per second). Alternatively, a collector comprising parallel electrodes can be used to achieve alignment. For the purposes of drug delivery systems, alignment is not generally necessary, however, and the majority of the examples discussed in this volume use simple flat-plate detectors. When scaling electrospinning up for industrial applications, conveyor belt-type collectors are required to allow continuous manufacturing; we will discuss these more in Chapter 7.

2.6.5 Other considerations

Most commonly, research on electrospinning is carried out in laboratories on the benchtop. Care must be taken when doing this because many of the solvents used for preparing polymer solutions smell unpleasant, and some are harmful. A robust risk assessment is thus required, but because the volumes of solvents used are small and the dispensing rates low there are normally no problems spinning in a well-ventilated laboratory. However, because humidity, temperature and the surrounding speed of air flow have a major influence on the electrospinning process, the ambient conditions and the location of experiment need to be monitored and recorded throughout to ensure it can be reproduced. Equipment exists which can precisely control temperature and humidity, but this often costs more than $5000 and requires a large isolated space (around 2 m^3) to house the cumbersome and bulky apparatus. Both these factors are usually highly inconvenient for many research labs. A simpler alternative is to procure a simple temperature and humidity meter and monitor these quantities throughout experiments to ensure reproducibility.

When preparing polymer solutions for spinning it is necessary to ensure that the polymer fully dissolves in the solvent to yield a solution with appropriate properties (in terms of conductivity and viscosity). Achieving this can require extensive optimisation. Solution preparation, together with other important considerations for a successful experiment, will be considered in detail in Chapters 3–5 as they differ somewhat for the different spinning processes.

2.6.6 Establishing and troubleshooting an electrospinning process

A more detailed discussion of how to set up and optimise fibre production will be provided in Chapters 3–5 for single-fluid, coaxial and triaxial, and

side-by-side processes, respectively. An excellent overview of the steps to be followed can be found in an instructive video article by Leach *et al.*[44]

2.7 Fibre properties

The fibres produced by electrospinning can be made from a wide variety of polymers, with very different drug release properties. For instance, the use of a fast-dissolving polymer such as PEO can accelerate the rate at which a drug gets into solution. Alternatively, a slow-dissolving or water-insoluble polymer such as poly(lactic-co-glycolic acid) or poly(ε-caprolactone) will give extended release, while a pH-sensitive polymer such as poly(methacrylic acid-co-methyl methacrylate) can be employed to target release to the small intestine by exploiting the changes in pH in the different parts of the body. Complicated architectures can be prepared through multi-liquid processing, and the diameter, porosity and mechanical properties of the fibre mat can all be tuned by systematic variation of material and processing parameters. These properties all lead to the products of electrospinning having a wide range of potential applications in the drug delivery field.

2.8 Characterisation

As described in detail in section 1.4, the first characterisation performed on an electrospun product is generally a simple visual inspection of a few fibres collected on a glass slide. If fibres can clearly be seen, then they can be inspected under a microscope to check if the process is optimised (are the fibres linear, or are beads present? Are there any particles or droplets present?). Once small quantities of good-quality fibres have been prepared, a larger batch can be produced. Typical characterisation for this would include scanning electron microscopy to check the fibre morphology, with transmission electron microscopy, focused ion beam microscopy and/or confocal microscopy often also undertaken to check for internal structure, particularly in the case of fibres from coaxial or multi-axial spinning. The ImageJ software (freely available from https://imagej.nih.gov/ij/) can be employed to quantify the fibre diamaters. The physical form of the drug and polymer is usually investigated with X-ray diffraction and differential scanning calorimetry, and infrared spectroscopy

is used to study the functional groups present in the fibres and any interactions between components. Thermogravimetric analysis can be performed to check for the presence of any residual solvent in the fibres; if solvent does remain and this is problematic, then the fibres can be stored in a desiccator or vacuum oven to remove this.

Depending on the intended application, it may be necessary to evaluate the mechanical properties of the fibres, and in the majority of cases drug release will be quantified through dissolution experiments. Permeation studies and *in vivo* work may also be appropriate if all the previous assays give promising results.

2.9 Summary

In this chapter, the EHD process has been introduced and explained. A brief discussion of the fundamental physics behind electrospinning has been presented, followed by a detailed discussion of the parameters which can affect the process and the nature of the influence they have. The requirements to establish a successful electrospinning experiment to generate defect-free fibres have been described. As a result, the reader should now have a good grasp of the overarching principles of electrospinning. Subsequent chapters will describe the different processes in more detail and explore the applications of the fibres produced.

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