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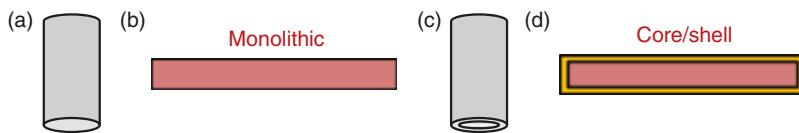
## Coaxial and multi-axial electrospinning

### 4.1 Introduction

As discussed in [Chapter 2](#) (section 2.6.3), coaxial electrospinning (also known as co-electrospinning) involves the use of a two-needle spinneret, with one needle nested inside another in a concentric fashion. The rapid stretching and solvent evaporation in electrospinning mean that the structure of the spinneret is propagated into the fibre products: thus, where the single-liquid, monoaxial, electrospinning process gives monolithic fibres, the arrangement of needles in coaxial spinning most commonly produces core/shell materials. This is depicted in [Figure 4.1](#).

The first report of coaxial electrospinning in the literature appeared in 2003.<sup>1</sup> In this work Sun *et al.* described the spinning of systems where both the core and shell comprised poly(ethylene oxide) (PEO), in addition to materials comprising PEO (shell)/poly(dodecylthiophene) (core), PEO/polysulfone and poly(L-lactic acid) (PLLA)/palladium acetate.<sup>1</sup> It was noted in this work that it is possible to use solutions which are non-electrospinnable for the core so long as the shell solution is amenable to processing by electrospinning, thereby significantly broadening the range of materials which can be handled. It was subsequently found that non-electrospinnable solutions can also be used as shell liquid when paired with an electrospinnable core solution, as elaborated in section 4.9. Since the work by Sun *et al.*, there has been an explosion of interest in using coaxial electrospinning to prepare drug delivery systems.

Coaxial systems have a number of potential benefits over the monolithic fibres produced in single-liquid spinning. These include preventing the initial burst of release commonly seen with monolithic fibres, or



**Figure 4.1** Schematic illustrations of the spinnerets used for, and products generated by, monoaxial and coaxial electrospinning.

(a) A single-liquid spinneret for generating (b) monolithic fibres; (c) a coaxial spinneret, which results in (d) core/shell products.

delivering more complicated release profiles. Release can also be targeted to different parts of the body or particular cell types, and multifunctional fibres loaded with multiple active ingredients can be prepared. Proteins, which often degrade in single-liquid spinning owing to their fragile three-dimensional structures, can be processed, as can cells. Each of these will be discussed in turn below. In addition, as mentioned in [Chapter 2](#), the shape and morphology of an electrospun product also depend on the material properties. By varying the properties of the working material, the use of a coaxial spinneret also enables the formation of a variety of other structures, including bubbles, scaffolds and multilayered fibres and particles.<sup>2</sup> Scientists have further sought to add additional liquids to the process, and we will finish the chapter with a discussion of three-liquid (triaxial) and four-liquid (quad-axial) processes.

## 4.2 Experimental considerations

The experimental set-up required for coaxial spinning was introduced in [Chapter 2](#) (section 2.6). As for single-liquid spinning, to achieve a successful outcome it is necessary to consider carefully the properties of the solution and the processing parameters in the coaxial setting. The major considerations are the same as for single-liquid spinning (see section 3.2), but there are additional factors to take into account with coaxial spinning.

### 4.2.1 Handling two liquids

There are two fluid interfaces in the coaxial set-up: the liquid–gas interface between the sheath solution and the surrounding air, and the liquid–liquid interface between the two working solutions. Optimisation of the fluid interfaces is key in the formation of a stable compound cone jet, which in turn is critical for achieving uniform and reproducible

core–shell products. The properties of the two solutions being processed cannot be considered in isolation. Although only one of the liquids (most commonly the sheath) needs to be electrospinnable, it is generally easier to achieve stable coflow if the two liquids have a relatively similar rate of solidification. If they do not, then there is a risk of one solution evaporating much faster than the other. This can cause clogging of the needle, and/or result in the separation of the two liquids. In turn, this leads to the properties of the fibres changing as a function of time during spinning, or separation of the core and shell fibre parts.

The charge distribution in a coaxial electrospinning jet is dependent on the properties of the core and sheath liquids. To form a cone shape as a compound droplet at the spinneret exit, at least one of the two liquids should enable a sufficient flow of charge. This is the driving liquid. In a typical monoaxial electrohydrodynamic process, the charge is localised at the interface between air and the charged liquid forming the Taylor cone. In a coaxial set-up, if the electrical relaxation time (time taken for an electron to travel in a material) of the sheath liquid is faster than or comparable to that of the core liquid, charges are localised at the outer interface between the sheath and the air, and the sheath liquid is the driving liquid. The core liquid can also act as the driving liquid if the outer is electrically insulating (a dielectric). In this case, when the driving interface is the inner one, the motion of the core liquid transmits to both the core and the sheath liquids via viscous force, setting the compound liquid in motion to form a coaxial jet.<sup>3</sup>

When the outermost sheath polymer solution has sufficient viscoelasticity, fibres with an encapsulated core are produced – this is coaxial electrospinning (or co-electrospinning). Hard-to-electrospin solutions or salts can be made into fibres by coaxial electrospinning, with a readily spinnable polymer serving as a template sheath for the core. If desired, the carrier polymer can be removed at a later stage. If the outermost sheath liquid does not allow sufficient molecular entanglement, coaxial electrospraying occurs, leading to core–shell particles.

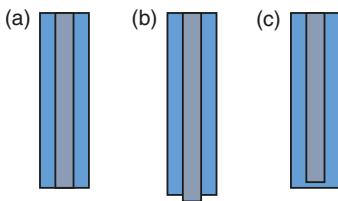
As noted above, the integrity and reproducibility of the core–shell structure require simultaneous and concentric break-up of the compound jet. The relative behaviours of the two liquids will hence significantly impact the integrity of the core/shell structure in the fibres. The miscibility of the two liquids must be considered, as must volatility: a large difference between the boiling points of the solvents used can compromise the integrity of the core/shell structure generated during product solidification. Defects such as porous structures or molecules from the core leaching into the shell layer can arise if the core and shell solvents are

miscible and evaporate at markedly different rates.<sup>4</sup> Careful consideration of the solvents available and optimisation of the interfacial compatibility are required in order to ensure the desired fibre products are generated.

The importance of flow rate has already been discussed in section 2.5.2; in coaxial spinning, the relative flow rates of the core and the shell liquids must also be considered. The faster the core flows with respect to the shell, the larger the core component of the fibres is expected to be. This tunability can be useful in varying the drug release profile, as will be discussed later. However, there is only a certain range of core-to-shell flow rate ratios over which the spinning process will be successful. At high core flow rates, there will not be a sufficiently fast rate of sheath solvent flow to encapsulate the core, leading to droplets with the two solutions mixed, or phase separation. The appropriate core-to-shell flow rate ratio is dependent on whether the core or the shell liquid is responsible for carrying the electrical charge (the driving liquid). Most commonly, when the shell liquid is the driver, a core-to-shell flow rate ratio of between around 1:3 and 1:10 is generally reported to give successful fibre formation, with lower ratios often (but not always) giving particles or mixtures of particles and fibres.<sup>5</sup> Higher ratios of 1:15 have also been reported to yield fibres successfully, however.<sup>6</sup> The exact range of ratios suitable for a particular experiment is dependent on the nature of the solutions used for the core and sheath, and needs investigation for each formulation being developed. The flow rate of the driving liquid carrying the charge also strongly affects the range of applied voltages that maintain the cone jet mode: higher flow rates of the driving liquid allow more charge to be carried per unit time and require a higher applied voltage to maintain a stable cone jet.

#### 4.2.2 The spinneret and electrodes

The coaxial spinneret is conceptually simple, comprising one (narrower) needle nested inside another (Figure 4.1(c)). The exact diameters of the needles used can be varied, but in the authors' experience, we have had success using inner-needle internal diameters of 0.21–0.35 mm and an outer needle of 0.84–1.2 mm. Most researchers work with the ends of the two needles in line. However, the exact positions of the needles (does the inner needle protrude from the outer needle, and if so by how much, or vice versa?; Figure 4.2) can have an influence on the process, as illustrated by Sofokleous and co-workers.<sup>7</sup> These researchers found that having the inner needle displaced inside the outer needle by a small amount (2 mm in their systems) led to more homogeneous products and better encapsulation of the core inside the shell. Lee *et al.* have similarly developed what



**Figure 4.2** Possible needle configurations in coaxial electrospinning, showing (a) the inner and outer needles inline; (b) the inner needle protruding from the outer; and (c) the inner needle nested inside the outer.

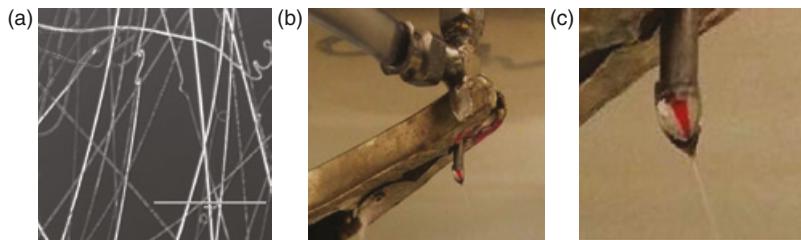
they termed a ‘core cut’ nozzle where the terminus of the core needle is inside the shell needle, similar to [Figure 4.2\(c\)](#), and found that it reduced jet instability and gave more control over the spinning experiment.<sup>8</sup>

Most researchers use standard blunt-ended dispensing tips for electrospinning, but several studies suggest that covering the end of the needle with a plastic (e.g. Teflon or poly(vinyl chloride)) coating can be helpful. This is thought to reduce the attraction between the ejected polymer solution and the exterior of the needle, and can thereby reduce the formation of semi-solid substances on the syringe and the concomitant clogging which often arises.<sup>9</sup>

In the most common coaxial experiment, the spinneret is connected to the positive electrode of the high-voltage supply and the collector is connected to the negative electrode or grounded. Under a high electric field, the inner and outer liquids in the coaxial jet may separate or break into indistinct layers. This arises due to flow instability during the evaporation of solvent as the jet travels towards the collector. Practically, it is often difficult to stabilise a compound cone jet when the interfacial liquid properties are less than optimal. In this situation, the stability of the coaxial cone jet can be improved by the addition of grounded or negatively charged ring electrodes placed at specific distances away from positive coaxial spinneret positive polarity.<sup>10</sup> This approach has recently been proven powerful in coaxial electrospraying; since electrospraying and electrospinning differ only in the viscoelastic properties of the working liquids (see [Chapter 2](#)), improvements in the apparatus design and assembly for electrospray are usually applicable for electrospinning.

#### 4.2.3 Establishing a coaxial process

The best place to start with developing a new process is to find a literature precedent which uses a similar polymer system. There exists a wealth of



**Figure 4.3** Optimising the fibre production process. (a) Fibres collected on a glass slide. Clear fibres can be seen, with no evidence for beads-on-string morphology. Some of the fibres are rather curved, however, which might be resolved by additional optimisation. Using a dye in the core liquid can aid visualisation of a coaxial process, as shown in (b) and enlarged in (c); a distinct two-liquid Taylor cone can be seen here, with the dye confined to the core liquid and no obvious liquid mixing. ((a) Courtesy of Alexandra Baskakova; (b and c) courtesy of Ukrit Angkawinitwong.)

information on single-liquid processes in particular, and thus a thorough review of the literature will likely reveal a protocol for a similar system to the one of interest. Using the closest possible literature parameters as a guide, we recommend initially spinning the two liquids singly and evaluating the fibres produced. If only one liquid in the process being developed is spinnable, then of course only this should be explored. The initial evaluation can be very crude, comprising simply collection of a few fibres (5–20 s of spinning or so) on a glass slide (or across a piece of cardboard with a hole cut in the middle) and holding them up to the light. If fibres have formed, this will be immediately obvious unless the fibres are below 400 nm in diameter. A more detailed assessment can then be undertaken by optical microscopy (**Figure 4.3(a)**).

Once fibres have been formed, a systematic variation in the voltage, spinneret-to-collector distance and flow rate for the single-liquid process is desirable, to observe which values give the best fibres. The products can be assessed by optical microscopy, and ideally will comprise fibres only with no particles/droplets. These fibres should possess uniform diameters, and no ‘bead-on-string’ morphologies should be visible. The optimisation process should be undertaken for each of the core and shell liquids. Coaxial electrospinning can then be commenced with the best set of parameters identified (or a compromise if very different parameters are found for the core and shell liquids).

In order to observe the behaviour of the liquids during initial coaxial experiments, it can be helpful to incorporate a small amount of

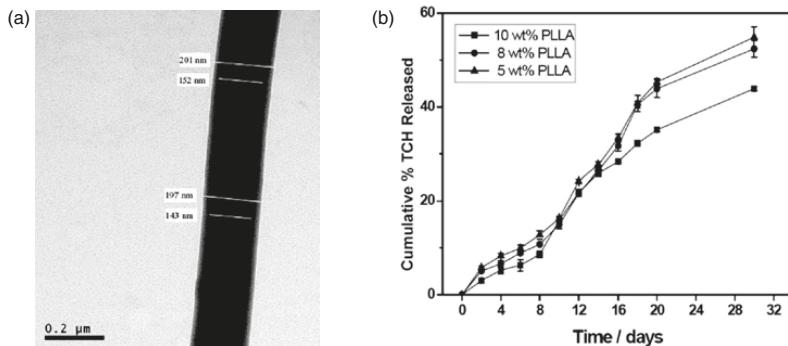
a dye into the core liquid. This aids visualisation of the Taylor cone, and thus whether or not there is a compound cone with the core liquid nested neatly inside the shell can be established quickly ([Figure 4.3\(b\) and \(c\)](#)). Again, collection on to a glass slide or cardboard window will enable any fibres formed to be seen immediately, and can be followed by optical microscopy evaluations. If the dye is fluorescent, then in favourable instances (i.e. with large-diameter fibres) it will be possible to observe the core–shell structure using fluorescent light microscopy. Once the experimental parameters have been adjusted to obtain the best-quality fibres (see above) then the preparation of a larger-scale batch of fibres can commence. This should be followed by a detailed characterisation by scanning and transmission electron microscopy (SEM and TEM), X-ray diffraction, infrared spectroscopy, and so forth.

## 4.3 Extended-release systems

### 4.3.1 Preventing burst release

A standard approach to extending the time over which drug release from a polymer nanofibre occurs is to use a slow-dissolving or insoluble polymer in single-liquid spinning. However, a major problem which arises with single-liquid electrospinning is that, as a result of the very high surface-area-to-volume ratio of the fibres, a relatively large amount of the incorporated drug is present at or near the fibre surface. This commonly results in a *burst release*, where a significant proportion of the drug content is freed rapidly into solution at the start of the process.<sup>4, 11</sup> The initial burst is then usually followed by a tailing-off of the release rate. The burst release is not a problem when developing a fast-dissolving drug delivery system, because the aim is to release all the drug content into solution in a few seconds or minutes. It is, however, a major issue where modified-release systems are concerned.

The core/shell structures which can be obtained through coaxial electrospinning offer one potential solution to this issue. By preparing a two-compartment fibre, where the shell comprises a blank polymer and the drug is in the core alone, the problem of significant amounts of drug being present at the surface should be resolved if the shell polymer is insoluble or slow-dissolving. One of the first studies to investigate this possibility came from He and co-workers, who prepared fibres with a PLLA shell and a core comprising the antibiotic tetracycline hydrochloride (TCH) mixed with a low quantity of PLLA.<sup>12</sup> A small amount of a cross-linking agent was added to the shell solution to improve the mechanical



**Figure 4.4** (a) Transmission electron microscopy image of a poly(L-lactic acid) (PLLA)/tetracycline hydrochloride (TCH) fibre prepared using a 10% w/v PLLA solution as the shell and a 5% w/v TCH/1% w/v PLLA core solution, and (b) TCH release from core/shell fibres prepared by He *et al.*<sup>12</sup> with the same TCH/PLLA core but varied concentrations of PLLA in the shell solution. (Adapted with permission from He, C. L.; Huang, Z. M.; Han, X. J.; Liu, L.; Zhang, H. S.; Chen, L. S. ‘Coaxial electrospun poly(L-lactic acid) ultrafine fibers for sustained drug delivery.’ *J. Macromol. Sci. B* 45 (2006): 515–524. Copyright Taylor & Francis 2006.)

properties and overcome the brittleness inherent to PLLA fibres. PLLA is a slow-degrading polymer (with a complete degradation time of more than 1 year under physiological conditions), and was employed because the aim of this work was to prepare antibacterial fibres for suturing or wound-dressing applications. TEM data showed the fibres to have clear core/shell structures (Figure 4.4(a)), and they were able to provide extended release over *ca.* 1 day. The production of core/shell systems in this work<sup>12</sup> additionally precluded the burst release previously reported from monolithic TCH-loaded fibres,<sup>13</sup> as shown in Figure 4.4(b).

Similar poly(lactic-co-glycolic acid) (PLGA) core/shell fibres, with both compartments made of PLGA and TCH in the core only, have been produced.<sup>14</sup> PLGA is another relatively slow-dissolving polymer (complete degradation time usually  $\geq$  2 months under physiological conditions), but despite this the fibres prepared showed a considerable burst release. The extent of the latter could be tuned by varying the polymer concentrations in the respective compartments, but it is clear that simply making a fibre with a shell of a slow-dissolving polymer and a drug-containing core does not necessarily prevent a burst release.

Coaxial electrospinning to produce fibres with TCH in the core has additionally been explored by Ramakrishna's team,<sup>15</sup> who prepared fibres with a PLGA (shell) and gum tragacanth (core). The core/shell fibres were found to be able to prolong the release period compared to monolithic fibres made from a blend of the two polymers, and also reduced the initial burst of release observed with the latter.

Analogous results have been seen for fibres comprising a poly( $\epsilon$ -caprolactone) (PCL) shell and a core of resveratrol (an antioxidant) or the antibiotic gentamicin sulfate, where drug release could be extended for more than 160 h.<sup>16</sup> PCL dissolves very slowly (over around 3 years *in vivo*), and thus these results are as intuitively expected. However, such findings are not ubiquitous. Hollow fibres were prepared consisting of a PCL shell with PEO and dexamethasone (an anti-inflammatory glucocorticoid) in the core, and despite the shell comprising PCL, a significant amount of burst release was observed.<sup>17</sup>

The observation that making fibres with a slow-dissolving shell does not necessarily prevent a burst release is well established in the literature. Such findings have been seen for systems with a polymer shell and drug-only core, for instance poly(L-lactide-co- $\epsilon$ -caprolactone) (PLCL) (shell)/heparin (core) fibres<sup>18</sup> and PLCL (shell)/paclitaxel (core) materials.<sup>19</sup> In both cases, despite the fact the drug was only present in the core, a notable burst release was seen.

A number of other authors have observed this phenomenon when using a drug/polymer matrix as the core solution rather than a simple drug solution, such as in the work of Zhu *et al.*<sup>20</sup> In this study, the authors used poly(lactic acid) (PLA), PCL or PLGA as the shell and a flurbiprofen axetil (non-steroidal anti-inflammatory drug)/poly(vinyl pyrrolidone) (PVP) blend for the core. Again, a large burst release was seen. The reasons behind such burst release are not entirely clear, since all of PLA, PLGA and PCL are slow to dissolve/degrade, but may arise as a result of some blending of the core and shell liquids, and/or the loaded drug being able to diffuse through pores in the shell.

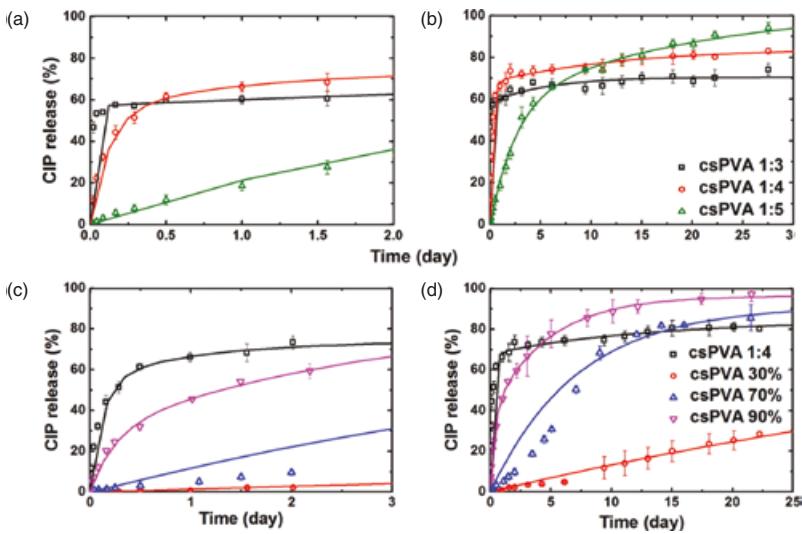
The problem of burst release is particularly acute when working with hydrophilic active ingredients and biodegradable matrices, and Venkatraman's team have explored the use of coaxial spinning to ameliorate this issue.<sup>21</sup> Metoclopramide hydrochloride (MtpH; used for the treatment of nausea and vomiting) was used as a model active ingredient, and fibres prepared with PCL, PLLA and PLGA shells and a poly(vinyl alcohol) (PVA)/MtpH blend in the core. Significant amounts of burst release were observed with monolithic fibres spun from each of PCL, PLLA and PLGA. The coaxial PCL/PVA system reduced this

burst somewhat, but a considerable amount of release was nevertheless observed in the first 6 h of dissolution testing. This was attributed to the presence of pores in the PCL shell. The coaxial PLLA/PVA and monolithic PLLA fibres behaved very similarly, which was believed to be because diffusion through the PLLA was the rate-limiting step to release, and the PLLA shell was not porous. The greatest difference in behaviour was observed with the PLGA systems, where the burst release was much suppressed in the coaxial fibres. In this instance, the rate of MtpH movement from the PVA core to the shell was the rate-determining step to release, and diffusion through the PLGA phase was relatively fast.

The work of Venkatraman *et al.* is important because it shows that merely making a core/shell fibre with drug located solely in the core and a slow-dissolving or insoluble shell is not sufficient to preclude burst release. It is important to consider the difference in hydrophilicity between the two polymers in the fibre; a moderate difference is required, because too great a difference may lead to a hollow core, as noted by Dror *et al.* (this arises because a very sharp interface forms between core and shell).<sup>22</sup> The drug itself needs to be more soluble in the core than the shell, and it is vital to control the electrospinning parameters to keep to a minimum the porosity of the shell (the ability of pores in a blank polymer shell to accelerate the rate of drug release from the core was also noted by Nguyen *et al.*<sup>23</sup>). Finally, the rate of drug diffusion through the shell needs to be considered: this should be relatively rapid, otherwise there is no benefit of using a core/shell system and no improvement in performance will be seen over a monolithic fibre of the shell polymer.

Zupančič *et al.* have built on these concepts, preparing fibres with an insoluble poly(methyl methacrylate) (PMMA) shell and a core of PVA or PVA/PMMA blends.<sup>24</sup> The core was loaded with the antibiotic ciprofloxacin, and the fibres proposed as advanced treatment modalities for a range of bacterial infections. The release rate could be tuned by varying the shell and core liquid flow rates and through the variation of the PMMA:PVA ratio in the core. In the optimal formulations, a burst release can be completely avoided and nearly zero-order release over a few days can be achieved (Figure 4.5).

A number of other studies have investigated drug-loaded core–shell fibres for extended release. For instance, a mixture of cellulose acetate (CA) and gelatin has been used to form the shell of a coaxial fibre loaded with the antibiotic amoxicillin and poly(ethylene glycol) (PEG) in the core.<sup>25</sup> Extended release over 1400 min was observed, with only a small burst release. However, it should be noted that the experiments were



**Figure 4.5** Tuning the rate of ciprofloxacin (CIP) release from core–shell poly(methyl methacrylate) (PMMA)/poly(vinyl alcohol) (PVA) fibers. (a) and (b) show the influence of varying the ratio of the core:shell flow rate from 1:3 to 1:5 in the preparation of PMMA (shell)/PVA (core) (csPVA) systems. (c) and (d) depict the release profiles of fibres prepared at a 1:4 core:shell flow rate and with a PMMA/PVA blend core (percent values refer to the percentage of PVA in the core). (a) and (c) show the early stages of the release experiment, and (b) and (d) the full time period studied. (Adapted with permission from Zupančič, S.; Sinha-Ray, S.; Kristl, J.; Yarin, A. L. ‘Controlled release of ciprofloxacin from core–shell nanofibers with monolithic or blended core.’ *Mol. Pharm.* 13 (2016): 1393–1404. Copyright American Chemical Society 2016.)

conducted in a simulated gastric fluid at pH 1.2 throughout, not really representative of physiological conditions in the body.

In other work, Wang *et al.* have made core/shell PLLA/poly-(3-hydroxy butyrate) fibres with the enzyme inhibitor dimethyloxalylglycine in the core.<sup>26</sup> Again, by doing so they could make significant strides towards ameliorating burst release by localising the drug away from the release milieu.<sup>26</sup> Increasing the thickness of the fibre shell led to slower release in this work.

Further examples of coaxial electrospun core/shell fibres being exploited to reduce or preclude a burst release include those loaded with epidermal induction factors for skin regeneration,<sup>27</sup> the broad-spectrum antibiotic bacitracin,<sup>28</sup> the antiviral drug acyclovir,<sup>29</sup> silver nanoparticles

for antibacterial applications,<sup>30</sup> dipyridamole to prevent platelet aggregation and reduce stroke risk<sup>31</sup> and tenofovir<sup>32</sup> or maraviroc<sup>33</sup> for anti-human immunodeficiency virus (HIV) treatment. The latter study employed ethyl cellulose (EC) as the shell and a PVP core, and found it was possible to tune the release rate by varying the shell thickness, with a thicker shell extending the release time. Similar results have been found with chitosan (shell)/PVA (core) fibres loaded with doxorubicin in the core,<sup>34</sup> and zein (shell)/zein-allyltriphenylphosphonium bromide (core) materials.<sup>35</sup>

There also exist reports of more sophisticated systems designed to sustain release and prevent the initial burst release. For instance, fibres have been prepared in which levofloxacin (an antibiotic) was first loaded on to mesoporous silica nanoparticles, and these in turn spun into the core of PCL fibres (with PCL comprising both the core and shell polymer).<sup>36</sup> A small reduction in burst release resulted from this system, and sustained release over more than 10 days was achieved. The use of the silica nanoparticles additionally extended the period of time over which the formulation was effective in preventing bacterial growth.

#### 4.3.2 Biphasic release

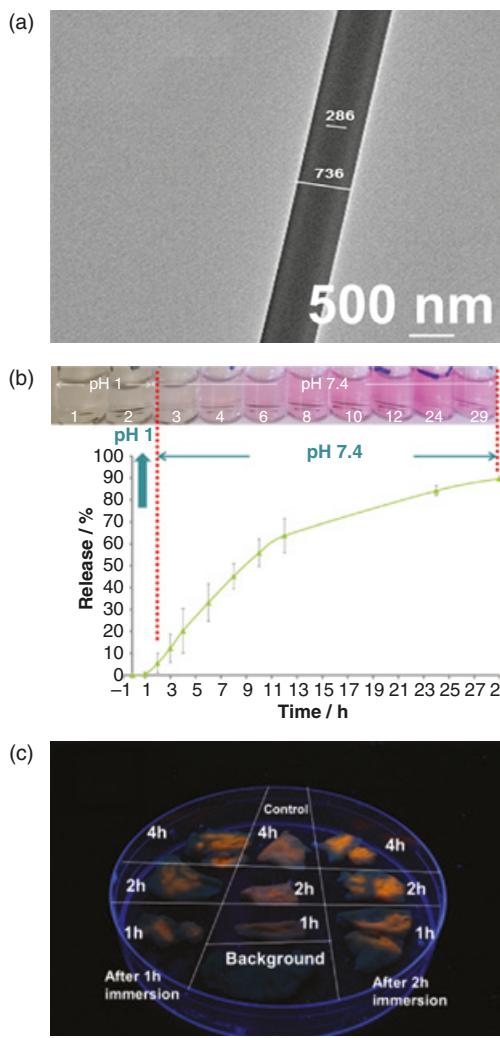
Although it is commonly desirable to prevent a burst of release in the initial stages of dissolution, on occasion, and if it is properly controlled, such rapid release early on can be beneficial. This is because it can provide a *loading dose*, rapidly increasing the blood plasma concentration of drug into the therapeutic window. If a second, sustained, phase of release then ensues, a therapeutic concentration can be maintained over an extended period. This has been achieved on several occasions using core/shell electrospun fibres, and involves using an insoluble or slowly dissolving polymer as the core, and a fast-dissolving polymer for the shell. The drug is present in both phases. This concept has been demonstrated using the non-steroidal anti-inflammatory agent ketoprofen as a model drug, PVP as the shell polymer and either zein<sup>37</sup> or EC<sup>38</sup> as the core. When the fibres are added to the dissolution medium, the shell rapidly dissolves and frees its drug content into solution for the loading dose. The drug in the core is then released over a prolonged period of time. By varying the drug concentration in the different phases or the flow rates of the core and sheath liquids<sup>38</sup> it is possible to tune the amount of release in the first and second stages. Other work has used fibres with a CA shell and a core containing sodium hyaluronate and naproxen-loaded liposomes to achieve such a biphasic release profile.<sup>39</sup>

The above studies use a single-fibre formulation to deliver biphasic release, but it is also possible to achieve this by combining two different sets of fibres. Ball *et al.* have used this approach with core/shell fibres comprising an EC shell and PVP/maraviroc core.<sup>33</sup> Different fibres were prepared with varied shell/core thicknesses and then two formulations, one faster-releasing and one slow-releasing, physically mixed to provide a loading dose followed by sustained release of the remaining embedded drug.

#### 4.4 Targeted drug delivery

Core/shell fibres generated by coaxial electrospinning have attracted attention for targeting the location of drug release in the body. In its simplest embodiment, this has taken the form of preparing fibres with the shell made of a pH-sensitive polymer (e.g. a Eudragit) which is insoluble at low pH. Such systems are designed for oral administration with the aim of preventing release in the stomach, where the shell is insoluble. Once the fibres enter the higher-pH lower parts of the intestine then the drug loading will be freed at a rate which can be controlled by judicious choice of the core polymer. For instance, fibres have been reported by Jin *et al.* in which the shell comprised Eudragit S100 (which dissolves at pH > 7) and the core made of PEO loaded with either gadolinium (III) diethylenetriaminepentaacetate hydrate or rhodamine B (Figure 4.6(a)).<sup>40</sup> The intention behind this work was to deliver an imaging agent locally to the colon for diagnosis of, for instance, irritable bowel syndrome. The authors found that the Eudragit coating successfully prevented almost all release in the pH conditions typical of the stomach, and upon an increase in pH to 7.4 (typical of the small intestine) the embedded functional ingredient was released in a sustained manner (Figure 4.6(b)). The imaging agents were unaffected by the electrospinning process, and were thus capable of imaging the colon, as was demonstrated *ex vivo* (Figure 4.6(c)). This approach was further extended to fibres loaded with both a drug and imaging agent for simultaneous imaging and drug delivery (so-called theranostic applications).<sup>41</sup>

However, as was noted for fibres designed to preclude a burst release, simply making core/shell materials with the exterior compartment made of a pH-sensitive polymer such as Eudragit will not necessarily result in the prevention of release in the stomach. Attempts to make such systems with 5-fluorouracil (5-FU; an anticancer drug) as

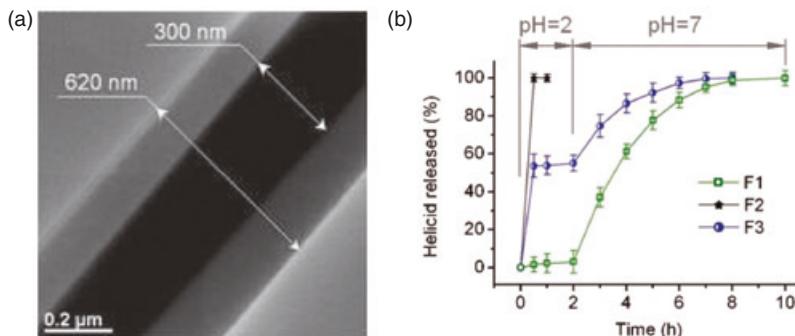


**Figure 4.6** Data demonstrating the utility of core/shell poly(ethylene oxide)/Eudragit fibres loaded with rhodamine B in the core as colon-targeted imaging systems. (a) A transmission electron microscopy image of the fibres; (b) the rhodamine B release profile under varied pH conditions mimicking passage through the intestinal tract; (c) a photograph taken under ultraviolet light showing imaging of porcine colon by the fibres after they had been immersed in phosphate buffer to remove the Eudragit shell. The central column (control) is where a 50 ppm rhodamine B solution was added to the colon, while the left and right columns show results obtained after the fibres were placed in phosphate-buffered saline for 1 and 2 h, respectively, before being transferred to the colon sections. (Reproduced with permission from Jin, M.; Yu, D. G.; Wang, X.; Geraldes, C. F.; Williams, G. R.; Bligh, S. W. ‘Electrospun contrast-agent-loaded fibers for colon-targeted MRI.’ *Adv. Healthcare Mater.* 5 (2016): 977–985. Copyright John Wiley, 2016.)

the active ingredient failed, for example.<sup>6</sup> Fibres were generated with a blank Eudragit S100 shell and a drug-loaded core formed of PVP, EC, Eudragit S100 or drug alone. Clear core/shell morphology could be seen by TEM, yet in all cases significant amounts of release were seen at pH 1.0. This arose even though the drug was only present in the core, and the Eudragit sheath is insoluble at pH 1.0. The authors ascribe this to the low molecular weight of 5-FU and its relatively high solubility under acidic conditions, proposing that these drive it to diffuse through pores in the shell and escape into solution. The release profiles observed show an initial burst of release at pH 1.0, followed by a second burst when the pH is raised to 6.8. While these are potentially useful, they are not the colon-targeted profiles which the researchers hoped to achieve.

Similar results have been obtained by Yu and co-workers, although by design in this instance.<sup>42</sup> A Teflon-coated spinneret was employed here to aid the electrospinning process (see section 4.2.3 above), and fibres prepared with a Eudragit L100-55 (soluble at pH > 5.5) core and PVP sheath.<sup>42</sup> Helcid, an extract from Chinese herbal medicine commonly used to treat headaches and insomnia, was present in both parts of the fibre. The materials were shown to give an initial burst release (loading dose) of the drug at pH 2 (representative of the stomach), followed by sustained release at pH 7, as illustrated in Figure 4.7. This arises because the PVP exterior dissolves very rapidly at all pH conditions, freeing the drug in the shell. Further release at pH 2 is prevented because the core is insoluble, but once the pH is raised the core too becomes soluble and the remainder of the drug is freed.

Other researchers have adopted innovative ways in which electrospun core/shell systems can be used to target release. Zhou's group performed an elegant study in which they first synthesised a folate-conjugated PCL–PEG copolymer, then assembled this into micelles with the anticancer drug doxorubicin, and finally spun the micelles into the core of PVA (core)/gelatin (shell) fibres.<sup>43</sup> This was designed as an implantable device. The folate conjugation on the micelles enables them to target cancerous cells selectively, avoiding any damage to non-cancerous tissue. The systems were found to be able to release the doxorubicin incorporated over a prolonged period of time (> 100 h). During *in vivo* studies, application of the fibres directly to a tumour led to high local concentrations of the drug but low systemic levels, helpful in minimising side effects. Selective internalisation of the micelles to cancer cells was realised, ensuring low toxicity to normal tissue.



**Figure 4.7** Using core/shell fibres to give targeted biphasic release.

(a) Transmission electron microscopy image showing the two-compartment structure of poly(vinyl pyrrolidone) (PVP) (shell)/Eudragit L100-55 (core) systems with helicid loaded in both compartments.  
 (b) Dissolution data for monolithic PVP/helicid (black) and Eudragit/helicid (green) fibres, together with the core/shell systems (blue). (Reproduced with permission from Yu, D.-G.; Liu, F.; Cui, L.; Liu, Z.-P.; Wang, X.; Bligh, S. W. A. ‘Coaxial electrospinning using a concentric Teflon spinneret to prepare biphasic-release nanofibers of helicid.’ *RSC Adv.* 3 (2013): 17775–17783. Copyright Royal Society of Chemistry, 2013.)

## 4.5 Multifunctional materials

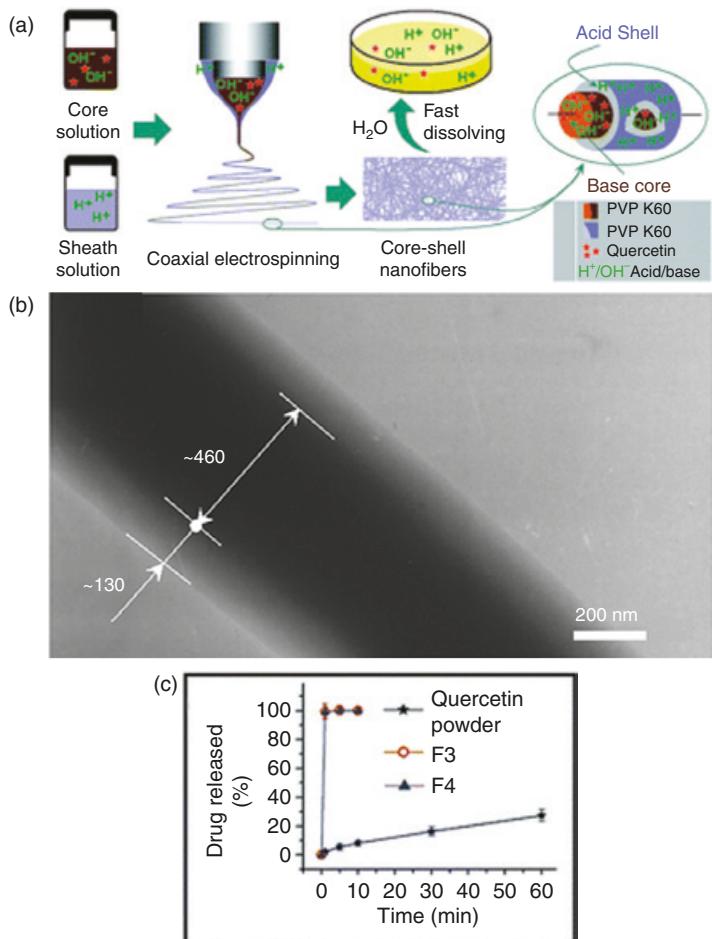
The core/shell architecture of fibres from coaxial spinning naturally lends itself to the production of multifunctional materials, with different functional components loaded in the two compartments of the concentric structure. One of the earliest reports of this came from Ramakrishna’s group, and explored the co-delivery of two model drugs, rhodamine B and bovine serum albumin (BSA) from PLCL fibres.<sup>44</sup> Electrospinning was performed using PLCL as the shell and a drug solution in the core, and the location of the two active ingredients was varied systematically. Unsurprisingly, the drug in the shell was released much more quickly than when incorporated in the core. An initial burst of release was seen in all cases, but this was reduced when the drug was loaded in the core of the matrix. Dual drug release systems have also been prepared in which vitamin C and E derivatives were encapsulated in the core of fibres with a poly(acrylonitrile) shell, with potential applications in the protection of skin from ultraviolet light.<sup>45</sup>

Another possibility is to incorporate additional excipients into the fibres. A flavour enhancer can be incorporated to mask the taste of bitter

drugs, for example. Alternatively, surfactants could be added to solubilise poorly soluble active ingredients and/or enhance permeation through biomembranes. In one example of such work, fibres were prepared consisting of a PVP/acyclovir core and a PVP/sucralose/sodium dodecyl sulfate (DDS) shell.<sup>46</sup> Acyclovir is a potent systemic antiviral active ingredient, but suffers from poor solubility. In the fibres generated, it is present in the amorphous form, which leads to much faster dissolution than the pure drug powder. Sucralose is added as a sweetener to hide the metallic taste of the drug, and DDS acts as a permeation enhancer. As a result of the latter, increased permeation through the porcine sublingual mucosa (*cf.* the drug alone) was observed. The same approach of a PVP/sucralose shell and PVP/drug core has also successfully been implemented with helicid.<sup>47</sup> Similarly, PVP-quercetin/PVP-DDS core/shell fibres have been prepared.<sup>48</sup>

Multifunctional materials are of particular importance in tissue regeneration, and electrospun fibres have attracted some attention in this regard. Tang *et al.* prepared fibres with a core of PLGA/hydroxyapatite and a shell of collagen and amoxicillin.<sup>49</sup> The latter (an antibiotic) was intended to prevent infections occurring in wounds, and the core to promote bone growth. The drug release rate could be tuned by varying the collagen concentration in the shell liquid, and it was found that the core could effectively prevent the ingress of fibroblast cells, which is often an obstacle to successful bone regrowth.

For drugs which are acidic or basic (i.e. those which can donate or accept a proton), the pH at which dissolution happens will have a profound effect on solubility. Yan *et al.* have used core/shell fibres to enhance the solubility of quercetin, an acidic drug which is more soluble at elevated pHs.<sup>50</sup> Fibres were prepared with a PVP core containing quercetin and sodium hydroxide, and a shell of PVP and citric acid (**Figure 4.8(a) and (b)**). The components were all amorphously distributed in the polymer matrix, which exhibited much accelerated dissolution over the pure drug (**Figure 4.8(c)**). Inclusion of the NaOH in the core was believed to increase the solubility and dissolution rate of the drug since it would be ionised upon being freed from the fibres. This, combined with the amorphous nature of the drug in the formulation, raised the dissolution rate. Without the presence of the citric acid, the base in the core could have led to an increase in the pH of the dissolution medium (which *in vivo* would cause irritation or other side effects). The fact that an acid/base pair existed in the material, however, led to improved functional performance but no change to the pH of the medium.



**Figure 4.8** The preparation of acid–base pair solid dispersions using coaxial electrospinning. (a) A schematic of the approach used; (b) a transmission electron microscopy image of the core/shell poly(vinyl pyrrolidone) (PVP)–quercetin–NaOH/PVP–citric acid fibres; and (c) drug release data (F3 and F4 contain different amounts of quercetin). (Reproduced with permission from Yan, J.; Wu, Y.-H.; Yu, D.-G.; Williams, G. R.; Huang, S.-M.; Tao, W.; Sun, J.-Y. ‘Electrospun acid–base pair solid dispersions of quercetin.’ *RSC Adv.* 4 (2014): 58265–58271. Copyright Royal Society of Chemistry, 2014.)

## 4.6 Other applications

The above sections have all considered small-molecule drugs, and represent the major challenges to which coaxial electrospinning has been applied in this regard. There are additionally a few further applications which have been explored. As has been discussed previously (section 3.1), it is generally the case that electrospun fibres contain their functional components in the amorphous physical form. This is because the very fast solvent evaporation in the process causes the random molecular arrangement present in the starting solution to be propagated into the solid state, and because the polymer matrices in the fibres hinder recrystallisation. Dong's team have specifically looked at using core/shell fibres to prevent recrystallisation of the potent antimalarial drug artemisinin.<sup>51</sup> Conversion of the drug from the amorphous solid dispersion formed immediately after electrospinning to a crystalline material was found to be more rapid in monolithic blend fibres of PVP/CA/artemisinin than in coaxial systems with a PVP shell and CA/artemisinin core.

Core/shell fibres have been prepared with liposomes loaded in the core, in an attempt to ameliorate the stability issues which often plague liposomal formulations.<sup>52</sup> Emulsions have also been incorporated into the fibre core.<sup>53</sup> In the latter work by Viry *et al.*, the highly soluble drug levetiracetam (used for the treatment of epilepsy) was loaded into fibres with a PLGA solution acting as the shell liquid, and the core liquid comprising either a drug/PLGA solution or a water-in-oil emulsion with the drug in the dispersed aqueous droplets and the oil phase comprising a PLGA solution in dichloromethane. The emulsion fibres were able to extend the release time and reduce the amount of burst release seen at the early stages of the experiment.

Core/shell fibres have further been exploited for the self-assembly of magnetic chitosan nanoparticles with potential biomedical applications.<sup>54</sup> From fibres with a shell comprising PVP/chitosan and a core of PVP/Fe<sub>3</sub>O<sub>4</sub> nanoparticles, Wang *et al.* were able to generate composite chitosan/Fe<sub>3</sub>O<sub>4</sub> nanoparticles following addition of the fibres to acetone and drying.

## 4.7 Protein delivery systems

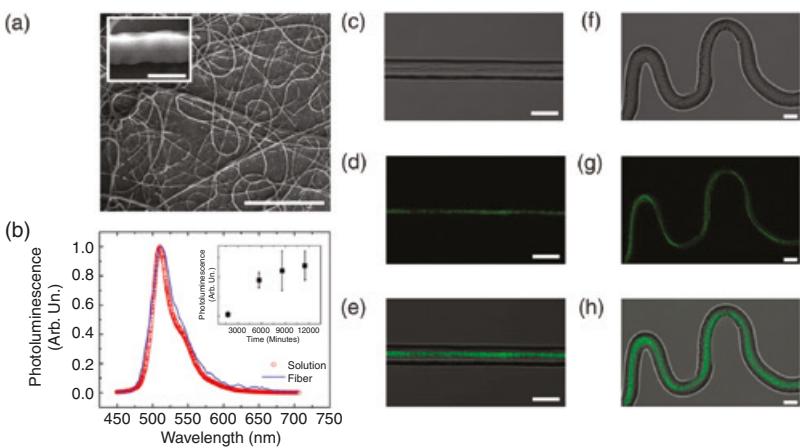
The small-molecule drugs discussed above can generally be processed by single-liquid electrospinning without problems, but it can be more desirable to prepare core/shell systems to deliver enhanced functional

performance. In the case of proteins, however, coaxial electrospinning is often a requirement. This is because the activity of proteins is very dependent on their tertiary structure (a three-dimensional structure involving different parts of these large molecules being folded together and anchored by intermolecular forces such as hydrogen bonding). This tertiary structure is easily disrupted, leading to a loss of activity (denaturation), and once it is lost often cannot be regained. Given the need to use volatile solvents in single-liquid electrospinning and the propensity of these to denature proteins, the single-liquid process often cannot be used to prepare protein-loaded fibres with acceptable activity.<sup>55</sup> Further, the low solubility of many proteins in the non-aqueous solvents used in typical electrospinning processes means that only very low doses can be loaded.<sup>55</sup>

To resolve these problems, researchers have adopted two principal approaches. One is emulsion electrospinning, with protein-containing aqueous droplets distributed in a continuous phase, as discussed in section 3.11.1. The second is preparing core/shell systems by coaxial spinning. In such materials the core comprises a protein solution in a buffer designed to preserve the tertiary structure, possibly also containing stabilising excipients such as trehalose. The shell is a polymer solution in a volatile solvent.<sup>55</sup> The potency of this approach was first demonstrated by Jiang *et al.*, who used a PCL shell and a core of BSA or lysozyme and PEG.<sup>56</sup> PEG was included because it is known to help stabilise proteins. The proteins were found to be unaffected by the electrospinning process, and through variation of the flow rate of the core solution the protein release profile could be tuned. Similar results have been seen from an analogous system but with dextran used instead of PEG in the core.<sup>57</sup> Other proteins to have been explored in coaxial spinning include the enzyme lactose dehydrogenase<sup>58</sup> and gelatin.<sup>59</sup>

Romano *et al.* recently reported an elegant study in which they used the E-green fluorescent protein to investigate the electrospinning and release of a biological active ingredient from core/shell PEO/PCL fibres.<sup>60</sup> The photoluminescence spectrum of the fibres was virtually identical to the raw protein, indicating that the electrospinning process did not affect E-green fluorescent protein functionality (Figure 4.9). Release was observed to occur over an extended time period of more than 200 h.

The pH of the core protein solution has been proposed to be important in maintaining protein stability. Angkawinitwong *et al.* explored the effect of varying the pH of the core solution on the stability for bevacizumab (an antibody potent for the treatment of cancer and age-related degeneration in the eye).<sup>61</sup> Fibres were prepared with PCL as



**Figure 4.9** Data for core/shell PEO/PCL fibres loaded with E-green fluorescent protein (E-GFP). (a) Scanning electron microscopy image (scale bar: 100  $\mu\text{m}$ ) with enlargement of a single fibre in the inset (scale bar: 1  $\mu\text{m}$ ); (b) photoluminescence spectra of raw E-GFP in solution (red) and in the fibres (blue), with an inset showing the release of protein from the fibres; (c–h) confocal microscopy images (scale bars: 5  $\mu\text{m}$ ) of the fibres showing the transmission (c, f), fluorescence (d, g) and merged (e, h) images. (Reproduced with permission from Romano, L.; Camposeo, A.; Manco, R.; Moffa, M.; Pisignano, D. ‘Core–shell electrospun fibers encapsulating chromophores or luminescent proteins for microscopically controlled molecular release.’ *Mol. Pharm.* 13 (2016): 729–736. Copyright American Chemical Society 2016.)

the shell and a core solution buffered either to the isoelectric point (pI) of the protein (the pH at which it is neutral) or a pH below this. At the latter pH, the protein bore a net charge during electrospinning, which led to degradation. In contrast, the fibres fabricated at the pI ensured that the bevacizumab remained intact. They also permitted a constant rate of release to be maintained over 60 days.

A number of researchers have compared fibres from monoaxial and coaxial spinning. One such study produced fibres with a PCL shell and a core containing a fluorescently labelled BSA and compared these with those prepared in a blend electrospinning process.<sup>62</sup> The core/shell system was found able to reduce the initial burst release during *in vitro* dissolution experiments, as also observed for small-molecule-loaded core/shell fibres (see section 4.3.1). Also working with PCL, Jansen’s team investigated the differences between single-liquid and coaxial

spinning of BSA and alkaline phosphatase.<sup>63</sup> The core/shell systems both extended release for longer periods of time and proved better able to maintain the biological activity of the protein.

A similar study compared these two processes in the preparation of PLGA fibres loaded with fibroblast growth factor-2 (FGF-2), known to be important in tissue repair and stem cell proliferation and differentiation.<sup>64</sup> The protein encapsulation efficiency and release profiles were similar for both types of fibres, with the monolithic fibres from single-liquid spinning releasing the protein somewhat more rapidly, as would be expected. Bone marrow stem cells were cultured on the fibres, but no clear conclusions could be drawn as to the relative efficacy of the two spinning methodologies in this regard.

Chitosan has also been explored as a filament-forming matrix for FGF-2, with both emulsion and coaxial emulsion (i.e. either the core or shell liquid is an emulsion) spinning compared as delivery systems.<sup>65</sup> No intact growth factor could be found in the monolithic emulsion fibres. In the core/shell case, inclusion of FGF-2 into the core rather than the shell of the fibres led to the presence of more intact protein in the formulation, in addition to improved cell adhesion and spreading. FGF-2 has further been incorporated into PCL (shell)/PEO (core) fibres.<sup>66</sup> Sustained release of the active ingredient over more than 9 days was observed.

There are a number of additional studies investigating core/shell fibres for the delivery of growth factors. For instance, Kong's group prepared materials with a PLCL shell and a core comprising dextran and platelet-derived growth factor-BB.<sup>67</sup> Smooth-muscle cells were cultured with the fibres, which were found to promote cell attachment and increase cellular activity.

In other work, nerve growth factor (NGF) has been incorporated into the core of PLCL shell fibres.<sup>68</sup> These materials were explored *in vivo* in rats, and found to have potential in promoting nerve regrowth.<sup>68a</sup> Similar fibres have been produced with PLA shells and silk fibroin cores loaded with NGF, and reported to aid the growth of the elongated neurite cells required for nerve growth.<sup>69</sup> Some authors have sought to prepare more sophisticated systems, in which the concentration of the NGF was varied through the thickness of the fibre mat.<sup>70</sup> The shell of the fibres comprised PCL, with a PEG/BSA/NGF core (BSA was added as a carrier protein and to help stabilise the NGF). A peristaltic pump was used to vary the NGF concentration in the solution used for spinning, such that the initial fibres collected contained a different NGF content to those collected at the end of the experiment. The side of the mat formed of fibres with the higher NGF concentration led to a higher percentage of

cells having neurite outgrowths. Sustained release of both NGF and BSA was seen.

Core-shell fibres with PLGA shells and PVA/transforming growth factor- $\beta$  (TGF- $\beta$ ) cores have been produced and compared with monolithic blend PLGA/PVA/TGF- $\beta$  fibres.<sup>71</sup> The core/shell fibres had potential in directing stem cell differentiation for the treatment of spinal injuries, and led to slower release of the loaded growth factor than the monolithic fibres. However, over the timescale studied they were less effective in promoting differentiation than the monolithic analogues.

Vascular endothelial growth factor (VEGF) has also been incorporated into fibres with a PLGA shell and a dextran/BSA/heparin/VEGF core.<sup>72</sup> VEGF was freed from the fibres over more than 25 days, with only a small burst release noted. Cells could spread effectively on the fibres, which additionally did not cause any undesirable immune response. Seyednejad *et al.* have further explored a mixture of the polyester poly(hydroxymethylglycolide-co- $\epsilon$ -caprolactone) and PCL as the shell and VEGF/BSA as the core.<sup>73</sup> The addition of the polyester helped to accelerate protein release, which is likely to be desirable since PCL degrades very slowly in the body (over 2–4 years). Again, the VEGF was found to retain its biological activity post-electrospinning.

Multiple bioactive factors may be incorporated into a single fibre, as demonstrated by Chen's group for TGF- $\beta$  and stem cell affinity peptide E7.<sup>74</sup> TGF- $\beta$  was loaded in the core of PCL (shell)/PVP-BSA (core) fibres, and the peptide subsequently covalently bound to the exterior. The presence of the peptide promoted the initial adhesion of stem cells, while the TGF- $\beta$  was freed from the matrices over around 20 days, maintaining its bioactivity throughout this time and promoting the differentiation of stem cells into cartilage cells. Such scaffolds hence have significant potential for connective tissue engineering.

Shalumon and co-workers have developed multifunctional growth factor-loaded fibres for bone regrowth.<sup>75</sup> Their materials consisted of a silk fibroin/chitosan shell loaded with nanosized hydroxyapatite particles, and bone morphogenetic protein-2 in the core. The release of protein from the core aided the differentiation of stem cells into osteoblasts and the presence of hydroxyapatite in the shell helped to direct bone growth. PLGA (shell)/collagen (core) fibres co-loaded with fibronectin and cadherin 11 – biomolecules known to be important in bone growth and cell adhesion – have additionally been reported.<sup>76</sup>

Other types of biomolecules which have been processed using coaxial electrospinning include a model virus,<sup>77</sup> which was incorporated into the core of PCL (shell)/PEG (core) fibres. These were found to release

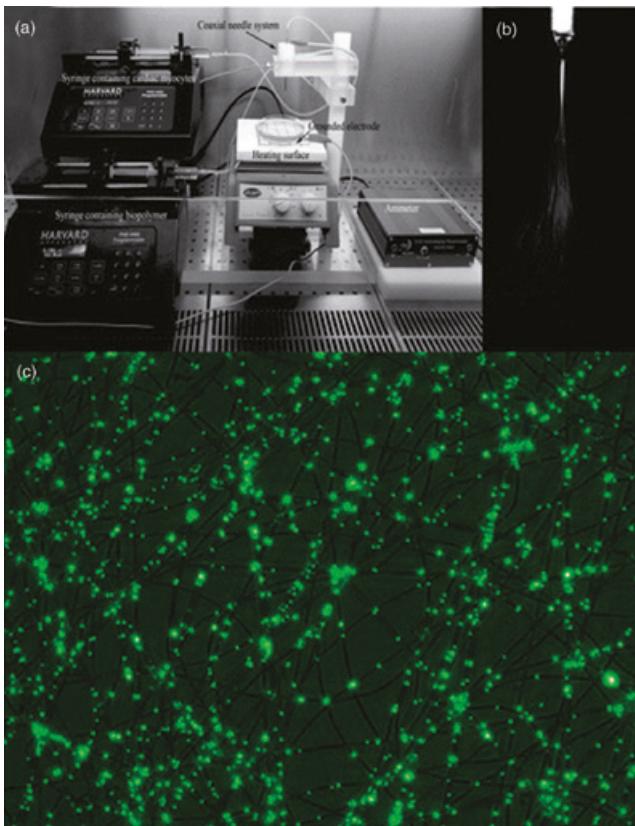
the virus over more than 2 weeks, and the released virus was determined to be less immunogenic than the unprocessed virus. These materials could have great potential in the development of viral gene delivery systems for a range of applications where defective DNA needs to be corrected, for instance in cystic fibrosis or severe combined immune deficiency. Non-viral genes can also be delivered through the coaxial electrospinning technology. For instance, plasmid DNA has been incorporated into the core of coaxial electrospun fibres.<sup>78</sup> A gene delivery vector was loaded into the shell of the fibres, which were shown to act as extended-release systems potent in cell transfection over a prolonged period of time.

## 4.8 Cell electrospinning

Beyond proteins and other small biomolecules, researchers have also found it is possible to process living cells through coaxial electrospinning. This field of research has been pioneered by Jayasinghe, with the first report in 2006.<sup>79</sup> A suspension of human 1321N1 astrocytoma (brain tumour) cells in culture medium at a concentration of  $10^6$  cells mL<sup>-1</sup> was used as the core liquid, with a poly(dimethylsiloxane) solution as the sheath. No statistical differences were observed between cell viability post-electrospinning and of control cells passed through a needle but without any potential difference applied. Follow-on work demonstrated that it is possible to process cells at very high concentrations of up to  $10^7$  per mL.<sup>80</sup>

Cell-loaded fibre mats have successfully been grafted into mice, and the ability of the cells to proliferate *in vivo* was found to be unaffected by the electrospinning process.<sup>81</sup> A range of cell types has been electrospun, with a number of resultant applications. For instance, cardiac myocytes have been spun into fibres with potential application in cardiac tissue engineering.<sup>82</sup>

In order to ensure that the cells remain viable post-spinning, the collector used for cell electrospinning needs to be considered carefully, and differs from the metal plates or cylinders most commonly employed. Collection is usually into a Petri dish or other container filled with a cell culture medium, with a grounded ring electrode placed above or below this. If required, a wire mesh can be inserted into the medium to provide a structure on which a scaffold can be constructed. Experiments are also usually performed in a laminar flow hood to ensure sterility. The apparatus commonly used is depicted in Figure 4.10, together with an image of electrospun cardiac cells.<sup>82</sup> It should also be noted that the polymers used for cell electrospinning must be highly biocompatible in order to



**Figure 4.10** Cell electrospinning. (a) The experimental set-up; (b) a photograph taken during the spinning process; and (c) a combined bright-field and fluorescence image of the cell-loaded electrospun scaffold. The cells can be seen in green and the fibre meshes in black. (Reproduced with permission from Ehler, E.; Jayasinghe, S. N. 'Cell electrospinning cardiac patches for tissue engineering the heart.' *Analyst* 139 (2014): 4449–4452. Copyright Royal Society of Chemistry 2014.)

maximise viability. This, and other, detailed experimental considerations are discussed in some recent reviews.<sup>83</sup>

## 4.9 Modified coaxial spinning

As discussed above, it was initially thought that for successful coaxial electrospinning a spinnable shell solution was required, while the core

liquid did not necessarily need to be processable alone by electrospinning. However, this is not always the case, and it turns out that a wide variety of non-spinnable shell solutions can be processed too. This can be achieved if the core liquid is a spinnable polymer solution,<sup>84</sup> or even a common solvent without a carrier polymer.<sup>85</sup> Working with an unspinnable shell solution has been termed *modified coaxial electrospinning* in the literature. It was first reported by Han and Steckl in 2009,<sup>84</sup> with the first application of the technique in drug delivery following in 2010.<sup>86</sup> The latter employed a pure solvent or solvent mixture as the sheath liquid, and very concentrated solutions of the PVP or Eudragit L100 polymers as the core, yielding monolithic fibres from a two-liquid process. Coaxial electrospinning was successful even when the core polymer solution was too concentrated to be electrospun in the standard single-liquid set-up.

This work was built upon to explore the influence of the shell solvent on the fibre properties (morphology, diameter, etc.), and the modified coaxial products were found to have reduced diameters and greater diameter homogeneity compared to analogous materials from single-liquid spinning.<sup>87</sup> A shell liquid comprising LiCl in *N,N*-dimethylacetamide (DMAc) has also been shown to be able to reduce the diameter of poly(acrylonitrile) (PAN) fibres, giving materials with smoother surfaces and reduced polydispersity.<sup>88</sup> The presence of a blank solvent or solvent blend outside the polymer core is believed to perform a number of functions, including reducing surface tension at the exit to the spinneret and slowing down the evaporation of the core solvent (by replacing the air/polymer solution interface with a solvent/solution interface).<sup>89</sup> This in turn can be helpful in preventing the formation of solid substances on the spinneret and subsequent blocking of the working liquid flow,<sup>90</sup> and hence it is possible to run spinning processes for much longer without manual intervention. Surfactant solutions can be used to similar ends.<sup>91</sup>

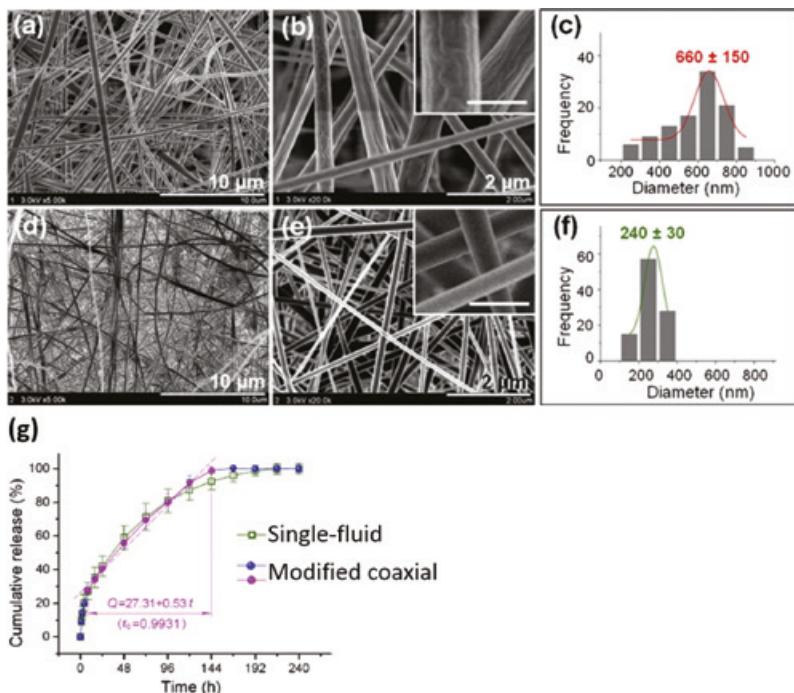
Such processes are of interest for drug delivery applications, because they offer new ways to tailor the arrangement of components in the fibres, and in particular the possibility of preparing in one step a polymer fibre with a functionalised exterior. For instance, using a solution of AgNO<sub>3</sub> as the sheath liquid and a PAN core solution, PAN fibres with AgNO<sub>3</sub> at the surface can be prepared.<sup>92</sup> Exposing these to ultra-violet light reduces the AgNO<sub>3</sub> to Ag nanoparticles, resulting in highly effective antibacterial materials. The benefit of the modified coaxial approach over the single-liquid monoaxial process is that it allows a functional ingredient to be localised at the surface; in this particular example, such localisation is very useful because any Ag trapped inside

the fibres would have no efficacy. By ensuring the Ag nanoparticles are only at the surface, there is no wasted material, which is beneficial in both cost and environmental terms. It is also possible to use a solution of a hydrophobic molecule such as stearic acid as the sheath, resulting in polymer fibres with a hydrophobic coating; this has been reported to improve the stability to humidity of PVP fibres, which usually are extremely hygroscopic.<sup>93</sup>

A direct comparison of ketoprofen-loaded CA fibres prepared by single-liquid electrospinning and those generated in a modified coaxial process with a mixture of DMAc, acetone and ethanol as the sheath liquid has been undertaken.<sup>94</sup> The modified coaxial fibres were found to be narrower and less polydisperse in their diameters than those from the single-liquid experiment, as shown in Figure 4.11(a)–(f). Both sets of fibres contained the drug in the amorphous physical form, and the dissolution profiles were similar (Figure 4.11(g)). However, the modified coaxial fibres showed more linear release between 8 and 144 h, and reached a higher overall release percentage. This indicates that the use of the sheath solvent has promise in preparing high-quality drug delivery systems.

Similar observations have been reported for zein/ibuprofen fibres,<sup>95</sup> and for Eudragit L100/sodium diclofenac materials using both blank solvent<sup>96</sup> and a salt solution as the shell.<sup>97</sup> A further study explored the preparation of fibres comprising CA and ferulic acid (an antioxidant commonly found in Chinese traditional herbal medicine), with PVP as an additional component.<sup>98</sup> The use of a blank sheath solvent reduced fibre diameter and improved polydispersity as before, and the inclusion of PVP helped to control the rate of drug release and ameliorate the problem of ‘tailing off’ (a slowing down in the release rate) which often arises with monolithic formulations. Analogous results were reported for systems comprising PAN/PVP and ibuprofen prepared using the modified set-up.<sup>99</sup>

Fibres prepared through the modified coaxial route have been explored as a template for self-assembly of solid lipid nanoparticles.<sup>100</sup> Materials were produced using PVP, tristearin and naproxen. Increasing the flow rate of the ethanol solvent used as the sheath liquid caused a reduction in the diameter of the composite fibres. When the fibres were added to water, the tristearin and naproxen spontaneously self-assembled into nanoparticles (see section 3.13), with narrower fibres resulting in smaller particles. These could play an important role in enhancing permeation through biomembranes, although no drug release or permeation studies of the self-assembled particles were reported.

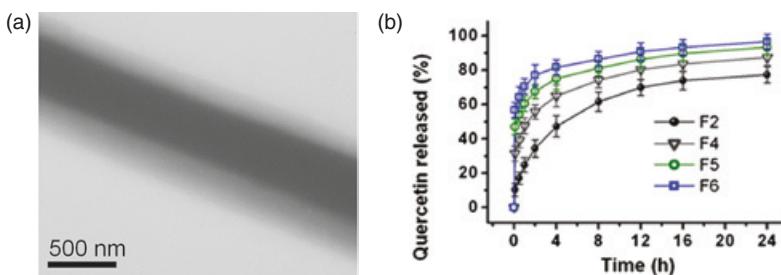


**Figure 4.11** A comparison of ketoprofen-loaded cellulose acetate fibres prepared by single-liquid and modified coaxial electrospinning. (a–c) Surface morphologies and diameter distribution of single-liquid fibres; (d–f) surface morphologies and diameter distribution of modified coaxial fibres; (g) dissolution profiles of the two sets of fibres. The scale bars in the insets of (b) and (e) represent 500 nm. (Reproduced 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.)

Biphasic release formulations have additionally been prepared from modified coaxial spinning. Here, the sheath solution is not a blank solvent or salt solution, but rather an unspinnable polymer solution. In one example of such work, Li *et al.* generated fibres using a spinnable EC/quercetin solution as the core and an unspinnable PVP/quercetin shell.<sup>9b</sup> They also used a poly(vinyl chloride) coating for the spinneret to aid the spinning process (see section 4.2.3 above). The

products comprised core/shell fibres (Figure 4.12(a)). The PVP shell dissolved very rapidly to release a loading dose of drug, while the EC core then gave sustained release. The amount of release in the first phase could be controlled by varying the drug content in the shell (Figure 4.12(b)). Similar findings have been noted with paracetamol as the active ingredient.<sup>101</sup>

Formulations with close to zero-order release have been prepared from modified coaxial spinning.<sup>102</sup> Experiments were undertaken with an unspinnable low-concentration CA shell solution and a spinnable higher-concentration CA/ketoprofen core. This led to fibres with a drug-loaded core and a shell of CA alone. The CA shell was able to ameliorate the burst release observed from analogous monolithic CA/ketoprofen materials, and thus provide a release profile close to being zero-order over 96 h. This approach has additionally been demonstrated for zein/ketoprofen systems.<sup>103</sup>



**Figure 4.12** Core/shell ethyl cellulose (EC)/poly(vinyl pyrrolidone) (PVP) fibres loaded with quercetin prepared by modified coaxial electrospinning. A series of fibres was prepared; formulation F2 comprises EC/quercetin fibres from single-liquid spinning, while F4–F6 are core/shell EC/PVP systems generated through the modified coaxial experiment, with increasing amounts of quercetin in the shell. (a) Transmission electron microscopy image of F5, showing the two-component architecture. (b) The results of dissolution testing, showing that increasing the amount of drug in the fibres leads to an increase in the percentage of release in the initial burst phase. (Adapted with permission from Li, C.; Wang, Z.-H.; Yu, D.-G.; Williams, G. R. ‘Tunable biphasic drug release from ethyl cellulose nanofibers fabricated using a modified coaxial electrospinning process.’ *Nanoscale Res. Lett.* 9 (2014): 258. Copyright Springer Ltd, 2014. This is an open access article.<sup>9b</sup>)

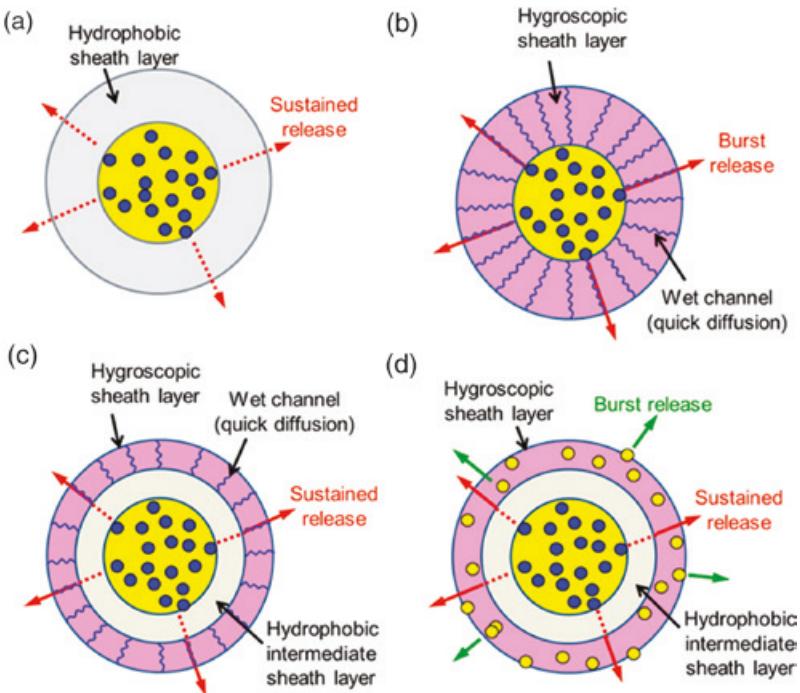
## 4.10 Triaxial and quad-axial systems

To produce high-quality multi-compartment fibres, it is necessary to ensure that there is no merging between the spinning solutions. This means either the compartmentalised solutions need to be immiscible or all the solutions need to lose solvent at similar rates: if one of the liquids dries faster than the others, then separation of the different compartments may arise. The first reports of triaxial electrospinning emerged from Lallave and co-workers<sup>104</sup> in 2007 and Kalra *et al.* in 2009.<sup>105</sup> The former report is concerned with using the resultant fibres to generate carbon nanotubes. The latter authors used silica in the core and outer layers. The middle layer comprised a block copolymer mixed with either magnetite nanoparticles or a second polymer, with the aim of making self-assembled structures in the confined space between the silica layers. Triaxial spinning has also been used to tune and optimise the mechanical properties of polystyrene/polyurethane-containing fibres.<sup>106</sup>

The earliest example of a triaxial drug delivery system emerged from the work of Han and Steckl, who made fibres containing PVP and PCL loaded with two dyes as model drug molecules (Figure 4.13).<sup>107</sup> The authors were aiming to overcome the problem of burst release that can arise with core/shell fibres if the shell is made of a hygroscopic (and therefore fast-dissolving) material. A hygroscopic shell is often desirable, however, in order to impart the fibres with good biocompatibility properties. A three-layer system with a drug-loaded core, hydrophobic middle layer and hygroscopic outer layer can combine both of these benefits (Figure 4.13).

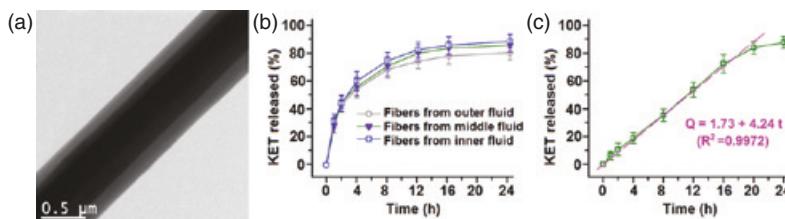
In Han and Steckl's work, they made some progress towards their goal by developing triaxial electrospinning and preparing materials with a hydrophobic exterior. Fibres were made with a core comprising PVP, and the middle and outer layers consisting of PCL.<sup>107</sup> Two different dyes were incorporated, one in the core and one in the outer layer. The latter dye was released very rapidly, while sustained release from the core was seen. By varying the dimensions of the inner, middle and outer needles in the spinneret, it was possible to modulate the rate of release from the PVP core, while the dye in the shell was freed similarly rapidly in all cases.

Yu and co-workers, mindful of the need for the liquids being processed in triaxial spinning to have similar properties, have generated three-layer fibres from three solutions of EC containing varying concentrations of ketoprofen, a non-steroidal anti-inflammatory drug.<sup>108</sup> The different concentrations of ketoprofen in each of the three



**Figure 4.13** Schematic showing the benefits of using triaxial electrospinning to prepare fibres which have a hygroscopic shell while preventing burst release of the incorporated drug. (a) A coaxial fibre with a hydrophobic shell will show sustained release, but may have poor biocompatibility, while (b) such a fibre with a hygroscopic shell will lead to rapid drug release, often obviating any benefits of the core/shell structure. (c) A triaxial system with a hygroscopic sheath can both give sustained release and ensure biocompatibility. (d) Drug could also be loaded into the outer layer of the fibres to deliver a loading dose. (Reproduced with permission from Han, D.; Steckl, A. J. 'Triaxial electrospun nanofiber membranes for controlled dual release of functional molecules.' *ACS Appl. Mater. Interfaces* 5 (2013): 8241–8245. Copyright American Chemical Society 2013.)

solutions resulted in fibres with a gradient distribution of the drug. The concentration of drug increased moving from the shell of the systems inwards. TEM images show that the fibres have a clear trilayer structure ([Figure 4.14\(a\)](#)), with all the components having the amorphous physical form.



**Figure 4.14** Data on the three-layer ethyl cellulose/ketoprofen (KET) fibres prepared by Yu *et al.* (a) A transmission electron microscopy image showing the internal structure of the systems; (b) the KET release profiles from monolithic fibres generated from each of the individual spinning solutions with different drug loadings; (c) the zero-order KET release profile of the three-layer fibres. (Reproduced with permission from Yu, D. G.; Li, X. Y.; Wang, X.; Yang, J. H.; Bligh, S. W.; Williams, G. R. ‘Nanofibers fabricated using triaxial electrospinning as zero order drug delivery systems.’ *ACS Appl. Mater. Interfaces* 7 (2015): 18891–18897. Copyright American Chemical Society 2015.)

As has been discussed previously, a major drawback with monolithic fibres is the initial burst of drug release which is typically seen. When monolithic fibres were prepared from the individual EC/ketoprofen solutions with different drug concentrations, such burst release was indeed observed (Figure 4.14(b)). The release profiles are virtually identical, regardless of the drug loading in the fibres. However, the three-layer fibres from triaxial spinning were found to give zero-order release over around 20 h, with a constant rate of drug release throughout this time (Figure 4.14(c)).

This release profile was realised by balancing three key factors. EC is insoluble in water, and thus drug release from this system will be controlled by the rate at which the ketoprofen molecules can diffuse out of the polymer matrix. Drug molecules in the shell of the fibre are very close to the dissolution medium and thus do not have to diffuse far to reach the solution. The shell also has the largest surface area of the three compartments. The ketoprofen molecules in the middle layer have to diffuse further to reach the outside of the fibres, and this layer also has a smaller surface area. If the drug concentration were the same in both the shell and middle layers, there would be more rapid drug release from the former. However, the increase in drug concentration going from the shell to the middle compartment compensates both for the increased diffusion distance and reduced surface area, leading to both

compartments having the same release rate. The same considerations apply to the core: again, the increased drug concentration compensates for the greater distance the ketoprofen molecules must travel to escape from the fibres and the further reduced surface area.

One of the major benefits of multi-axial electrospinning is that non-spinnable solutions can be processed so long as at least one of the liquids being processed is spinnable on its own. This has been well documented for coaxial electrospinning, and although less explored, initial reports suggest it is equally true for triaxial spinning.<sup>109</sup> Yang *et al.* successfully prepared fibres using a modified triaxial process in which the outer liquid was pure ethanol, the middle liquid a solution of Eudragit S100 and the core liquid a solution of lecithin and diclofenac sodium. Only the middle liquid here is individually spinnable, and the authors hence propose that a triaxial process can be undertaken with only one spinnable liquid so long as the two non-spinnable ones are not in contact.<sup>109</sup> The Eudragit/lecithin/diclofenac fibres were found to act as pH-sensitive drug delivery systems, with the Eudragit precluding release at acidic pH. At neutral pH, diclofenac was released in a novel two-stage process. Some drug was freed directly into solution upon dissolution of the Eudragit, but the majority of the drug and lecithin initially combined to form hydrophobic nanoparticles. These subsequently freed the embedded diclofenac, leading to both sustained release and increased permeation through the intestinal mucosa.

The modified triaxial approach has further been applied to prepare nanoscale drug depot fibres.<sup>110</sup> A solvent sheath liquid was employed to surround a CA middle layer, which in turn encompassed a core comprising a ferulic acid solution. This led to a system where partially crystalline ferulic acid was trapped inside a CA-based fibre. The release rate of the drug was controlled by its rate of diffusion through the CA, which resulted in close to zero-order release over around 36 h. These fibres showed reduced initial burst and tailing-off effects compared to monolithic CA/ferulic acid materials prepared from modified coaxial spinning. The drug depot fibres could not be prepared directly in coaxial electrospinning, because rapid solidification of the shell CA led to blocking of the spinneret.

Given the paucity of reports on three-liquid electrospinning, it is not surprising that relatively little work has been done to explore the effect of the processing parameters on the success of the process. However, some detail is known on the effect of solvent volatility and polymer molecular weight for systems of PCL and CA.<sup>111</sup> Fibres were prepared with a CA shell, PCL intermediate layer and a mineral oil core. The latter was then removed by dissolution in octanol to produce hollow materials. It was

found that for successful electrospinning it was important to have the outer working liquid composed of a more volatile solvent system than the middle liquid, and also for the molecular weight of the outer polymer to be greater than or equal to that of the middle polymer.

There are only a few reports of triaxial spinning in the literature so far. This is most likely due to the difficulty in equilibrating the multiple liquid interfaces and the rate of solvent evaporation in a concentric jetting process with three or more coflowing liquids. On the other hand, there has been much effort in generating multilayered particles via triaxial and multi-axial electrospraying, the sister technique of electrospinning. As described in Chapter 2, electrospraying and electrospinning use the same set-up and differ only in the viscoelastic properties of the working liquids, which are primarily determined by the polymer concentrations and molecular chain length. The solvent choices that are optimal for coaxial and multi-axial electrospray could be helpful for optimising solvent choices and the handling of multiple liquids in coaxial and multi-axial electrospinning. Interested readers are directed to Chapter 6, section 6.8, for discussions on electrospraying.

It is possible in principle to process four, five or even more liquids: the complexity of such processes increases rapidly with the number of liquids being processed, however, which explains why only one report of a four-fluid electrospinning process could be found in the literature.<sup>112</sup> In this work, Labbaf *et al.* used a four-needle (quad-axial) spinneret and electrospun four-layer core/shell fibres made of different biocompatible polymers: PEG, PLGA, PCL and poly(methylsilsesquioxane). The multilayered four-liquid electrospinning technique has significant potential in drug delivery applications, however, as it offers the advantages of achieving in one formulation the delivery of multiple active pharmaceutical ingredients in a time-dependent fashion as demanded by the course of treatment.

## 4.11 Conclusions

This chapter has introduced the concept of coaxial electrospinning, and provided some details on how to implement the experiment. We have then discussed the various ways in which the approach has been applied to drug delivery, including the prevention or reduction of burst release, giving biphasic or targeted release and preparing multi-functional materials. Its utility in processing more complex active biomolecules such as proteins, and even cells, has been considered, as has the modified coaxial electrospinning process where only the core is

spinnable. Finally, the possibilities of triaxial and quad-axial spinning and the layered materials it can produce have been enumerated. Overall, it is clear that multi-axial electrospinning offers the ability to generate increasingly complicated nano- and micro-scale architectures, with concomitantly enhanced functional performance. The caveat is that the experiment becomes increasingly complex as the number of liquids being processed increases; this is particularly important when consideration is given to scaling up the process. We will return to this topic in [Chapter 7](#).

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