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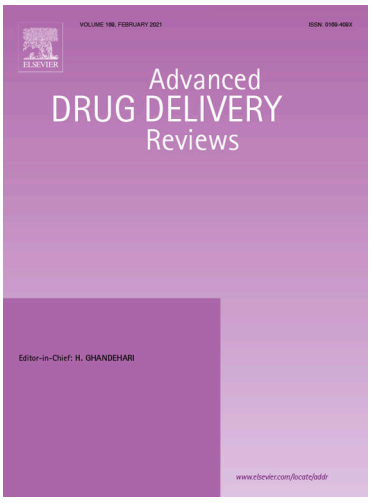

Recent Applications of Electrical, Centrifugal, and Pressurised Emerging Technologies for Fibrous Structure Engineering in Drug Delivery, Regenerative Medicine and Theranostics

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Recent Applications of Electrical, Centrifugal, and Pressurised Emerging Technologies for Fibrous Structure Engineering in Drug Delivery, Regenerative Medicine and Theranostics

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Highlights:

- In tune with the emergence of nanotechnology, the use of fibrous structures in drug delivery and regenerative medicine has increased exponentially in recent years.
- The development and application of engineering techniques to overcome the limitations of current fiber fabrication methods has been discussed here.
- Fabrication of fibers within the micro- and nanometer scale with complex and multifaceted capabilities is a major drawback of conventional fiber production methods.

Abstract:

Advancements in technology and material development in recent years has led to significant breakthroughs in the remit of fiber engineering. Conventional methods such as wet spinning, melt spinning, phase separation and template synthesis have been reported to develop fibrous structures for an array of applications. However, these methods have limitations with respect to processing conditions (e.g. high processing temperatures, shear stresses) and production (e.g. non-continuous fibers). The materials that can be processed using these methods are also limited, deterring their use in practical applications. Producing fibrous structures on a nanometer scale, in sync with the advancements in nanotechnology is another challenge met by these conventional methods. In this review we aim to present a brief overview of conventional methods of fiber fabrication and focus on the emerging fiber engineering techniques namely electrospinning, centrifugal spinning and pressurised gyration. This review will discuss the fundamental principles and factors governing each fabrication method and converge on the applications of the resulting spun fibers; specifically, in the drug delivery remit and in regenerative medicine.

Keywords: fiber engineering; drug delivery; regenerative medicine; tissue engineering; electrospinning; centrifugal spinning; pressurised gyration; nanofibers; biomedical; nanotechnology.

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1. Introduction

The current drive in pharmaceutics is aimed at providing improved healthcare delivery and the ability to predict, prevent and treat illnesses by targeting specific individual needs [1-4]. This is further revolutionising the practise of personalised medicine and opening new frontiers for novel technologies [5]. The ability to vary the structures of excipients during the engineering process offers exciting prospects due to the resulting impact on the functionality and performance of the final product or device [6-8]. In order to accomplish this, several engineering technologies have been deployed to achieve structural variations of the pharmaceutical dosage forms such as hydrogels [9-12], suspensions [13-15] and micelles [16-20].

Whilst these various structures have shown potential; the one structure that has shown most promise has been fibers. Fibrous or filamentous structures have gained significant attention in the last few decades in an array of remits ranging from drug delivery [21-28], tissue engineering [29-36], regenerative medicine [37-44] and even extending into the cosmetics industry [45, 46] and electromagnetics and thermal management [8, 47-52].

Fibers can be engineered on the macro, micro and nano scale, but the latter have been found to be more efficient systems for cellular and molecular applications compared to their macro (more than 1 mm) and micro counterparts; a testament to their high surface area to volume ratio and structural stability [53]. Currently, the use of fibrous structures on the nanoscale is on the incline; with a demand for such structures being in sync with the evolution of nanotechnology [50, 54]. They have been used for an array of applications including wound healing [55-58], drug delivery patches [59-63] and tissue engineering where for example they have been utilised in dental implants [64-66] and cell-based therapy [67-69].

With constant evolution in technology and material development, methods of fiber engineering are continuously being established. This article will be looking at the current methods of fabricating fibers and going into depth about some of the emerging technologies in this field and how these look to improve the application, productivity and efficiency of fiber engineering.

2. Current Fiber Engineering Methods

2.1 Wet Spinning

Wet spinning (WS) is a well-known industrial fiber engineering method that emerged in the 1930s [70] and has since been exploited not only in the pharmaceutics remit but also in the textiles sector [71]. Both synthetic and natural nano/microparticulate polymers have been fabricated using this technique with various therapeutic agents being loaded into these fibrous structures such as chemotherapeutics [72, 73], antibiotics [74, 75] and nonsteroidal anti-inflammatory drugs (NSAIDs) [76, 77].

The principle of WS is based on a non-solvent-induced-phase-inversion which fabricates fibers over a range of diameters [78]. Typically, a WS system consists of 4 key components (**Table 1, Figure 1a**). The first is an injecting system which can either by operated manually, via a syringe pump or by gravitational pull [79] and this introduces the second component (the polymeric solution) into the

system. Sometimes a heat exchanger may be employed as the polymer solution may need to be kept at specific temperatures that may be below or above ambient or room temperature. A standard WS set-up also comprises a spinneret and a coagulation bath containing a non-solvent for the polymers. The solution is extruded straight into the coagulation bath and during the spinning process, the solution is continuously injected and solidifies upon contact with the non-solvent [80]. More modern or complex developments of the method have seen computational control of the coagulation bath or the extruding needle [81].

The thermodynamic conditions of the three-component mixture (i.e. the polymer, the solvent and the non-solvent) and the coagulation kinetics in tandem affect the morphology of the resulting wet-spun fibers [82-84]. Fibers as small as several microns up to hundreds of millimeters have been yielded with WS with the diameter of the fibrous structures being controlled by three parameters: i) the viscosity of the polymeric solution being extruded through the system, ii) the injection rate and iii) the size of the spinneret [85]. Alongside being able to control the diameter of the resultant structures, another advantage of WS is the large pore sizes the fibers possess. These pores prove beneficial with regards to cell adhesion and cell penetration within scaffolds and films [78]. Despite these advantages, it is difficult to get aligned fibers with WS. Additionally, developing fibers on a nanoscale is very difficult.

WS is a simple, easy fiber engineering process and has been used to process an array of natural and synthetic polymeric material for a range of biomedical applications. It has been broadly used with natural polymers such as chitosan [86-89], collagen [75, 90, 91] and silk fibroin (SF) [71, 92, 93] which are particularly difficult to be processed with other fabrication techniques like melt spinning due to low thermal stability. One of the first reported uses of chitosan in WS was in 1993 by East and Qin [88]. Using a 2% aqueous acetic acid solution of chitosan, they successfully produced wet spun fibers that were used for precursor for subsequent processing.

Malheiro et al reported using a blend of poly(ε-caprolactone) (PCL)/chitosan for tissue engineering. With methanol as the coagulation non-solvent, they were able to yield fibers of which the diameters could be controlled and modified [87]. Scanning Electron Microscopy (SEM) analysis highlighted large pores on the surface of the fibers and a large degree of surface roughness, indicating enhanced cell attachment. Similarly, WS was used to develop chitosan fibers and 3D fiber meshes for potential use in tissue engineering applications [94]. The wet spun scaffolds were found to be suitable for cell ingrowth and did not inhibit osteoblast proliferation, highlighting their potential in bone tissue engineering.

In the case of SF, Ng et al used a custom coaxial spinneret to fabricate core-sheath wet spun SF-based fibers [93]. They used a 17% SF/polyurethane (PU) as the sheath solution and iota-carrageenan/polyacrylamide as the inner solution; yielding double layered hollow wet-spun structures and successfully improving the water absorbency of natural silk.

Several studies have also shown the potential of WS in fabricating drug-loaded fibers. A research group in Australia have shown how preparing fibers containing chitosan and alginate at various concentrations and antitumor agent gemcitabine hydrochloride via WS was a feasible approach for localised therapy of pancreatic cancer [72]. The 3D stability and biophysical properties of the wet spun structures allowed for high drug loading and controlled localised drug release.

Elsewhere, the *in-vitro* cancer activity of 5-fluorouracil (5FU) was controlled and sustained by suspending the hydrophilic drug in a hydrophobic polymer (poly (l-lactic acid)) (PLLA) [95]. The

suspension was extruded and solidified into isopropyl alcohol and it was found that fibers within 50 and 250 µm in diameter could be fabricated. The cancer activity could be controlled and sustained *in-vitro* for approximately three weeks; with the release kinetics being modified by adjusting process parameters such as polymer concentration, coagulation bath and injection rate.

Constant evolution in technology led to a development in WS which resulted in the computational controlled deposition of polymeric fibers in a predetermined design; fabricating 3D constructs; layer-by-layer in the coagulation bath [96]. Several studies of this method of computer-aided wet spinning (CAWS) have shown potential in manufacturing of polymeric (e.g. PCL [97]) scaffolds which resemble various anatomical sites; signifying an effective technique to tailor some of the key properties of the scaffold associated with morphology including drug release, kinetics and cell interaction [98, 99].

2.2 Melt Spinning

Melt spinning (also known as extrusion) is the technique most commonly used for the fabrication and production of commercial synthetic fibers. It is predominately used in the textile and polymeric industry [100].

As the name suggests, only polymers that melt easily can be utilised with this method of fiber production. During the process, the polymer is taken to its melting point and is extruded through a spinneret which comprises of micron-sized holes into a chamber (**Table 1**). A cold blast of air passes through the chamber; solidifying the viscous melt of polymer which is subsequently collected [101].

Melt spinning of fibers tends to be the most economical of methods due to no solvent needed to be recovered or solvent evaporation. Additionally, the spinning rate is also efficient and generally quite high. It is also possible to control the cross-sectional shape and the diameter of the fibers by altering the shape (e.g. round, hollow (**Figure 1b**), cross-shaped, star-shaped;) of the holes in the chamber the melt is passed through [102-104]. For example, Naeimirad et al demonstrated that fibrous structures could be developed and subsequently filled; yielding fibers with a liquid core [105]. Due to these micron-sized orifices, the diameters of the resulting fibrous structures rarely fall in the nanoscale region [105]. Melt spinning produce fibers of the largest diameters compared to all of the fiber producing techniques and this alludes to process parameters such as the spinneret orifice diameter, spinning temperature, extrusion rate and also physical liquid properties such as polymer viscosity [106].

Despite being predominately used in the textile industry, melt spinning's potential in drug delivery (e.g. antibiotics [107], NSAIDs [108]) and biomedical application (e.g. wound healing [109], tissue engineering [110]) has been noticed in recent years. Mangual et al developed a biodegradable poly (D, L-lactic-co-glycolic acid) (PLGA) stent which proved to exhibit comparable characteristics to similar existing magnetic stent materials [111] . The biodegradable stent was made of extruded PLGA fibers and contained iron oxide nanopowder; increasing the stents efficiency in implant-assisted-magnetic drug targeting.

The potential of melt spinning in tissue engineering was also seen when Wu et al developed poly glycolic acid (PGA)-PLLA fibers into a scaffold where human endothelial cells progenitor cells assembled like microvascular networks within the pores on the fibrous structures [110].

Antifungal agent clotrimazole was loaded into PCL fibers via the extrusion method yielding structures approximately 1 µm in diameter [112]. Both *in-vitro* and *in-vivo* analysis indicated extended activity of

the extruded fibers with the PCL-clotrimazole structures showing good antifungal activity for more than 21 days.

By using Solupus®, a polyvinyl caprolactame-polyvinyl acetate polyethylene glycol (PEG) graft copolymer, Nagy et al considerably improved the dissolution of steroidal antiandrogen sprinolactone [113]. This was owing due to the wettability of the Soluplus® fibers and the high surface area of the resulting fibrous structures.

2.3 Phase Separation

Phase separation is a fiber fabrication method based on thermodynamics primarily used to prepare fibrous scaffolds in tissue engineering since the 1980s [114, 115]. It is a simple technique which can utilised for both synthetic and natural materials and uses the thermally induced phase separation (TIPS) methodology [116]. However, it is possible to induce phase separation without the presence of a solvent [117]. The fundamental principle of phase separation is based on using polymers with different solubilities at different temperatures enabling them to separate into their respective solvents [116]. It is essentially a 4-step process whereby first the polymer(s) is dissolved into the solvent to achieve a homogenous solution (Table 1). A gel is subsequently formed from the solution and is maintained at the optimum gelation temperature. Following removal of the solvent, a complex matrix of fibrous structures remains which possesses a characteristically high degree of porosity. There are two types of TIPS: 'solid-liquid phase separation' and 'liquid-liquid phase separation'. The mechanism used is dependent on the crystallisation temperature or the freezing point of the solvent that is being used.

The biggest advantage of the phase separation process is that the resulting structure morphology can be altered and controlled by modifying physical liquid properties such as polymer type and concentration or by modifying process parameters such as freezing temperature [118]. Solid-liquid phase separation depends on the latter; the solvent crystallisation is much higher than in liquid-liquid separation causing the solvent to crystallise and the polymer to separate when the temperature is reduced. Upon removal of the solvent crystallites by sublimation, pores remain in the scaffold. By selecting phase separation process and specific solvents, the structure and size of the pores can be controlled [119].

The phase separation process has only been used with a select few polymers. For example, it has been found to be particularly useful in developing scaffolds based on PLLA systems for tissue engineering and regenerative medicine; as seen in **Figure 1c** [120-124]. Ma et al developed PLLA scaffolds using low polymeric concentrations and yielded fibers between 50 and 500 nm with high degree of porosity [122]. Similarly, PLLA scaffolds were successfully fabricated utilising liquid-liquid phase separation with porosity ranging from 80% and 90%; with the pores averaging between 20 and 60 μm in diameter [121].

The porous nature of these scaffolds makes them advantageous in tissue engineering applications. For example, Li et al developed 3D networks based on polyhydroxyalkanoate (PHA) polymers [125]. Using the TIPS method, fibers 50-500 nm in diameter were developed and when compared to PHA matrices made with conventional fiber engineering methods, the novel 3D networks showed vast improvements with respect to biodegradation and mechanical strength. These scaffolds successfully mimicked the microenvironment of extracellular matrix (ECM), allowing for improved cell compatibility thus making it a good candidate for tissue engineering or future implant development.

TIPS has found to be particularly advantageous in the realm of bone tissue engineering [126-129]. For example, Munir et al employed TIPS to engineer fibrous scaffolds comprising PCL and collagen type 1 [129]. They found by increasing collagen concentration, the porous structure of the scaffold could be altered. By utilising a collagen concentration of 0.2% w/v, the scaffolds demonstrated comparable properties to native cartilage: highlighting the potential of such devices for cartilage tissue engineering with easily tuneable porosity and compressive properties.

Despite being able to tailor the mechanical properties and control pore size, not all polymers can undergo phase separation due to the gelation step [130]. There are also issues with scale up and continuous production as this process is unable to yield long continuous fibers.

2.4 Template Synthesis

Template synthesis is a method used to prepare fibrous structures via pores in a hollowed membrane. Fibers based on polymers [131], metals [132] and ceramics [133] have been engineered using this technology. Using a mould or template made of a metal oxide (alumina), fibers are produced by extruding the polymeric solution through pores in the template under the pressure of water [134]. The extruded polymeric fibers are subsequently collected in a coagulation bath or in a solidifying solution. By altering the template and ultimately the pores in the mould, the diameter of the resulting fibers can be controlled (**Figure 1d**) [135]. Despite this, the fibers are that are fabricated tend to have large diameters and this is often determined by pore size [136]. The lengths of the fibers are also limited. Template synthesis is a multistep-process and requires a post-synthesis step where the template is removed, making the entire process time-consuming.

3. Emerging Fiber Engineering Technologies

3.1 Electrospinning

One of the most popular emerging techniques for fiber engineering is electrospinning (ES). In the last decade, the interest in ES, both in research and commercially, has increased exponentially due to its capabilities in a range of applications (e.g. drug delivery, tissue engineering, theranostics, textiles and the food industry [137, 138]) and in sync with the emerging remit of nanotechnology and the ever-evolving arena of material development [139, 140]. This has allowed the process of ES to constantly be scrutinised and industrialised; resulting in successful, complex developments in process set up and consequently complex structure engineering [141-149].

The fundamental principle of ES revolves around utilising an electrical field to atomise viscous polymeric solutions to produce fibrous or filamentous structures [139, 150]. Extensive research in this remit alongside advancements in material development has led to a variety of materials being used in the ES process [151]. Both natural (e.g. chitosan [152-156], collagen [157-160], SF [161-164], gelatin [165-170]) and synthetic polymers (e.g. PGA [171-173], poly lactic acid (PLA) [174-179], PLGA [180-188], poly vinylpyrrolidone (PVP) [77, 189-194], PCL [195-203]) have been spun to fabricate fibrous structures falling within the nanometer range for a wide range of applications [204].

Unlike more conventional methods of fiber fabrication, ES has the ability to reproducibly develop nanofibers in a one-step process at ambient temperatures [205].

3.1.1 Electrospinning Process and Set-Up

ES is a cost effective, one step process that is utilised to fabricate fibers on a micro and nanoscale [206]. The first concept of utilising electrical forces to develop one dimensional structures was established by Morton in the early 20th century [207]. Morton's work was predominantly dependent on the work of Zeleny [208, 209] and Taylor [210, 211]; both of which whose research paved the way for electrohydrodynamic atomisation (EHDA). Zeleny's work exploited the work of Lord Rayleigh which looked at the maximum charge a liquid droplet could "hold" before it become unstable. Zeleny demonstrated how electrostatics affect the behaviour of liquids [209] while Taylor's work experimented with physical properties of the solution; ultimately developing the underlying theory of EHDA. Using these base principles, a series of patents were filed by Cooley [212, 213] and Formhals [214, 215] which presented the foundations of the basic ES set-up that is seen in the present day. Formhals dedicated his research to the concept of ES, evolving the configuration of the system, resulting in a number of patents being issued. With the emergence of nanotechnology, the interest in the process spiked in the 1980s and has continued to do so; reflected in the number of publications which more than tripled in the period of 2005-2010 [54].

The basic ES set-up consists of 5 key components (**Figure 2a and 2b**): a syringe holding the polymeric formulation, a syringe infusion pump, a conductive processing needle/nozzle, a voltage supply and a collection plate. The polymeric solution is fed into a typically stainless-steel conductive needle and the infusion pump allows the flow rate of the polymeric solution to be maintained and controlled whilst the voltage supply applies an electrical field to the system. Once a Taylor Cone jet is established at the nozzle exit (via optimising solution flow rate and applied voltage), the jet experiences instability. In this regard there are three types of instabilities: Rayleigh instability, axisymmetric instability and non-axisymmetric instability [216]. The latter is the most crucial with ES as this is the main cause of fibrous structure generation [217]. With non-axisymmetric instability, an inverse cone may be observed, consisting of a single rapidly bending strand. In basic terms, the liquid jet does not break up but instead elongates to form continuous fine strands [218]. **Figure 2c** demonstrates the forces at play which act on the conductive needle to initiate the electrospinning process.

The ever-increasing process understanding in this remit has enabled the ES process to evolve, yielding complex and innovative systems; including coaxial systems containing multiple concentrically arranged needles (yielding multi-layered fibers) [186, 219-233] and electrohydrodynamic printing [2, 57, 142, 234-241]; enabling the fabrication of prepatterned, aligned fibers. An emerging development includes systems utilising a needleless approach; yielding fibers within the nanometer range without the use of a conductive nozzle [242-251].

3.1.2 Governing Principles of the ES Process

The ES process is affected by various parameters relating to the viscoelastic (polymeric) solution being spun and the process parameters [252]. It is governed by physical liquid properties such as viscosity, surface tension and electroconductivity. The voltage applied to the solution/system as well as the rate at which the liquid is expelled also has an impact on the jetting stability and the outcome of the ES process. By modifying and optimising these parameters, it is possible to tune the structures that are fabricated and engineer fibrous structures with desired diameters, surface charges, porosity and morphology [253].

3.1.2.1 Solution Properties

When selecting materials to fabricate fibers using ES; the physical liquid properties are crucial. Arguably, viscosity is the most important as this is what will determine fiber size (diameter) and morphology [254]. The stretching of the viscoelastic solution to form those rapidly bending strands is dependent on the viscosity of the solution. The viscosity of the solution will determine whether particles or fibers are formed at the nozzle exit. Extensive research has shown solutions with low viscosity do not have the ability to form fibrous structures where, in contrast, too high a viscosity results in system/nozzle blockage therefore reducing the efficacy of jet forming at the nozzle exit [255]. As a result of this, the viscosity must be optimised for the specific formulation in question. The viscosity is directly proportional to polymeric concentration; the higher the concentration the more difficult it is to control and maintain liquid infusion from the nozzle [256]. Hence, the maximum viscosity value has been stated to be 215 Poise [54, 254, 257, 258].

The break-up of the viscoelastic solution at the nozzle is a result of the electrical forces overcoming the surface tension of the solution [252]. The surface tension is a direct property of the solvent; which acts as the vehicle in the polymeric solution. Different solvents can present different surface tension values therefore when selecting materials for ES, it is imperative to consider this. Surface tension values need to be low enough to allow the electrical field to destabilise the liquid to form a jet. Too high values will reduce the efficiency of the process as this will not allow the liquid to break up appropriately and form continuous strands [259]. It has been suggested that the surface tension of the solution should not exceed 50 mNm^{-1} to allow the electrical field to effectively break up the polymeric solution to allow instability to occur hence producing fibers [260].

Due to the induction of the electrical field, there is an accumulation of charge at the nozzle jet; resulting in jet break up. For successful ES, the polymeric solution to be processed must be conductive in order for the electrical field to atomise the solution [261]. The electroconductivity of the final solution is a product of the polymers used and the solvent. One advantage here is that most polymeric materials exhibit adequate electroconductive properties. Solvents that exhibit low electroconductivity values will be unable to produce a stable jet and result in the formation of beaded fibers [262]. Liquids with high electroconductivity also demonstrate similar problems, exhibiting highly unstable jets leading to broad fiber size distribution [252]. Like with viscosity and surface tension, the material choice can optimise this parameter to produce thinner fibers. The ideal range for electroconductivity when ES is between 10^{-8} and 10^{-4} Sm^{-1} [204, 263].

3.1.2.2 Process Parameters

The most critical process parameter in ES is the applied voltage. A threshold must be reached before the jet experiences the characteristic instability to result in the whipping motion of the fibrous strands ejecting from the nozzle exit [264]. The electrical field applied to the system has found to have a substantial effect on the size of the resulting structures; with some researchers observing that higher voltages giving rise to broad fibers [265]. Contrastingly, some studies have found that utilising higher voltages resulted in the fabrication of fibers with small diameters and moreover narrow size distributions due to increased repulsive forces within the system [255, 266]. The induced electrical field needs to be sufficient enough to overcome the surface tension of the polymeric solution to be processed therefore this parameter needs to be optimised for the specific formulation in question. Increasing the strength of the applied electrical field can lead to multiple jets forming at the nozzle

exit resulting in polydisperse structures with wide size/diameter distribution [267]. Low voltages can result in intermittent jetting, inhibiting the production of long, continuous fibrous strands.

In order to form a stable Taylor Cone jet, it is imperative to optimise the flow rate or the infusion rate of the polymeric solution through the conductive needle [268, 269]. The flow rate is inversely proportional to the viscosity of the fluid; as flow rate increases, viscosity increases [270]. The rate which the liquid is expelled through the needle also affects the diameter of the resulting structures [271]. The slower the rate of liquid infusion, the smaller the diameter of the resulting fibers due to sufficient time to allow for solvent evaporation. High flow rates can result in topographical inconsistencies; leading to beaded fibers due to inadequate solvent evaporation before the fibers are deposited or collected.

Another parameter which has increasingly been noted to influence the resulting fibrous structures is the working distance between the nozzle exit and the collection plate [252]. Again, this is a factor that must be optimised for the specific formulation. By altering this distance, it is possible to control the size and the morphology of the resulting structures. This is because working distance directly affects the strength of the electrical field [272]. It has been reported that the working distance can affect the morphologies of the resulting fibers; too short a working distance there is not enough time to allow the solvent to fully evaporate resulting in wet samples being collected [273]. Therefore, the working distant must be far enough to allow full solvent evaporation but within reason to not lose sample to the surrounding atmosphere [274].

3.2 Centrifugal Spinning

Centrifugal spinning is an emerging fiber engineering technique which has gathered a lot of attention in recent years, both in research and commercially [275]. It is also known as rotary jet spinning. The basic principles of this method of fiber fabrication exploit the stretching of viscoelastic solutions due to centrifugal forces upon utilising optimised rotational speeds [276, 277]. By combining polymer chemistry and fluid mechanics, centrifugal spinning offers a method of engineering fibrous structures in a simple, cost effective process. The main advantage here is mass production and fiber alignment [278], promoting the use of the resulting fibers in an array of applications including drug delivery [278-285], tissue engineering [286-292] and energy [293-295]. The process boasts high production rates and abilities to process a large range of materials including polymers [278, 296-302] ceramics [303-307] and carbon [308-311].

3.2.1 Centrifugal Spinning Process and Set-Up

Centrifugal spinning is an innovative method which was first utilised in the fiberglass industry; engineering micrometer-sized glass fibers [312]. Extensive research and attention to the fundamental principles engaging with centrifugal forces to develop fine fibrous structures has led to many patents being proposed [313-315], subsequently leading to commercialisation of the process. For example, in 2009, Lozano and Sarkar developed a patented technology, namely Forcespinning™ which employs fast rotational processing spinnerets to fabricate fibers with narrow diameters [316, 317].

The set-up for centrifugal spinning was first proposed and patented in 1990 by Wagner et al where a disc with perforations was rotated at relatively fast speeds; allowing thermoplastic materials to be extruded via the perforations; fabricating fine fibers of molten glass or metals [318].

A typical set-up consists of 3 main components (**Figure 3a)**. The rotating reservoir (spinneret) holds the polymer-solvent solution and tends to be controlled by a motor. The reservoir, which is perforated,

is rotated at specific speeds, allowing the centrifugal forces to overcome the surface tension of the formulation, forming liquid jets (Taylor Cone) at the orifices on the spinneret [319]. Due to the combination of centrifugal forces and optimised rotational speeds, the jets are stretched and allow for full solvent evaporation; leading to the solidification of continuous fibrous structures which are subsequently collected on a stationary cylinder wall [320]. **Figure 3b** shows an example of a set up used to developed centrifugal spun fibers.

3.2.2 Governing Parameters of Centrifugal Spinning

With centrifugal spinning, there are 3 main forces at play: centrifugal forces, surface tension and viscoelasticity, as highlighted in **Figure 3c** [321, 322]. The morphology and size of the resulting centrifugally spun fibers will be determined by specific process parameters and the properties of the spinning solution [323]. By adjusting parameters such as spinneret rotational speed and orifice diameter and physical liquid properties such as viscosity and surface tension; it is possible to fabricate fibers of specific criteria.

3.2.2.1 Process Parameters

Both the rotational speed and the spinneret orifice size can affect the morphology of the resulting fibers [324]. While centrifugal force is the driving force in this process; rotational speed is essentially the limiting factor. Whilst rotational speeds from 2000 rpm to 3000 rpm are often used [325], to ensure the spinning liquid is emitted from the perforations to allow for jet formation and solution stretching, the rotational speed of the spinneret must reach a critical minimum speed to ensure that that the centrifugal forces are able to overcome the surface tension of spinning formulation [326]. Speeds below the critical minimum rotational speeds result in the centrifugal force not being able to overcome the surface tension of the solution to produce a jet at the orifices. Mathematical modelling has demonstrated that an increase in rotational speed enhances solution stretching, yielding thinner fibers [326, 327]. However, some research has shown that there is also a critical maximum rotational speed, which when surpassed, results in fibers of larger diameters due to insufficient time for solvent evaporation and inadequate jet stretching [328].

The diameter of the orifices has a direct effect on the morphology and the size of the centrifugally spun fibers. By altering and optimising this parameter, it is possible to control the shape and the size of the resulting structures. Whilst smaller diameters would theoretically result in “ultrafine” fibers; practically it is not so simple. Small diameters will restrict sufficient liquid flow hence producing thin fibers; however, using too small perforation diameters will exacerbate the viscous force of the spinning formulation. [329]

The diameter of the spinneret is another crucial process parameter to consider as this will affect size of the fibers being fabricated [330]. Increasing the diameter (whilst maintaining a constant rotational speed) will result in an increase in centrifugal forces enabling ease of solution extrusion thus resulting in decreased fiber diameter [331].

The collection distance (i.e. the distance between orifice and collection plate) needs to be assessed to ensure optimised flight time of the ejected, stretched jet. This distance needs to be sufficiently long enough to allow solvent evaporation before collection. Too small a distance and beaded fibers will be formed [332]. Increasing the distance will increase the flight time; enabling further jet stretching; yielding thinner fibers [333]. Typical collection distances are between 30 and 80 cm [332] however

optimised distance is based on the volatility of the solvent and the time taken for the solvent to evaporate as well as how long it takes for initiation of fiber fabrication.

Therefore, spinneret diameter, orifice diameter and collection distance must be optimised for the spinning solution in question.

3.2.2.2 Spinning Solution Properties

The formulation to be processed via centrifugal spinning typically consists of a polymer in the form of a solution or a viscous melt of the polymer. As a result of this, the viscosity and the polymer concentration are of extreme importance [330]. The viscoelastic properties of the materials being process has a direct impact on the solution's ability to fabricate and spin fibers. The viscosity of the solution can be controlled by altering the molecular weight and/or the concentration of the polymer(s); with the latter being the most convenient approach [326]. Highly viscous solutions will pose challenges as the driving force used to stretch the jet will not be strong enough to form the characteristic jet at the orifice. Consequently, gravitational forces dominate, holding the solution together and preventing extrusion of the liquid. In contrast, if the viscosity is too low, droplets will be engineered as opposed to fibers due to inadequate jet elongation [334].

Another key solution property is surface tension. In order to form a stable Taylor Cone at the orifices, the centrifugal forces need to be able to overcome the surface tension of the spinning solution [335]. Too high surface tension values will result in beaded fibers being formed due to inadequate forces to break up the molecules and allow for jet stretching. The surface tension can be tuned by modifying polymeric molecular weight and careful solvent selection. Incorporation of additives such as surfactants can also result in changes in surface tension; typically resulting in a reduction in surface tension [330].

3.2.3 Development of Centrifugal Electrospinning

An exciting advancement with centrifugal spinning is the introduction of an electrical field, namely centrifugal electrospinning. The technology here exploits the driving forces of both electrospinning (i.e. electric field) and centrifugal spinning (centrifugal force) which work in tandem and contribute to the stretching of the viscoelastic polymer solution, yielding highly aligned nanofibers [336, 337]. The factors governing the efficacy and efficiency of the process is similar to centrifugal spinning with an additional factor to consider. As with electrospinning, the applied voltage needs to be optimised for each formulation being processed [319]. The employment of the electrical field allows the rotational speeds usually required (i.e. up to 3000 rpm) to be reduced to as low as 300 rpm. Simultaneously, the use of the centrifugal forces eradicates the need for higher voltages to overcome the surface tension of the spun solution [338]. Utilising these two dominant forces results in high throughput engineering of fibrous structures within the nanometer range which could prove to be valuable in both the drug delivery and regenerative medicine remit [29, 339].

3.3 Pressurised Gyration

Pressurised gyration is a novel fiber fabrication technique which was first developed in 2013 [340] with research showing the use of pressure in fiber production dating back to 2006 [341]. The process utilises attributes from centrifugal spinning and includes the use of a pressurised gas to help extrude fibers. Despite the concept only being developed within the last decade, the application of the resulting fibrous structures spans a wide range of areas including drug delivery, tissue engineering, wound healing and diagnostics.

Based on the fundamental principles of pressurised gyration, many processes have been developed such as pressurised melt gyration, infusion gyration and pressurised-coupled infusion gyration. Pressurised gyration and all these extensions of the process have allowed for high production throughput and also ease of scale up [342, 343].

3.3.1 Pressurised Gyration Process and Set-Up

The process of pressurised gyration is based on the principles of Rayleigh-Taylor instability of the spinning polymeric solution. Here, it is thought the liquid-gas interface experiences instability due to differences in density upon the introduction of a working gas pressure [340].

There are 3 main components to the pressurised gyration set-up (**Figure 4a, 4b**). A cylindrical vessel, typically made of aluminium, contains narrow orifices or perforations to allow for extrusion of fibers. This metallic vessel is able to rotate by the aid of a motor which can achieve speeds of up to 36,000 rpm. Pressurised gas (nitrogen) (up to 0.3 MPa) is introduced to the system via a gas inlet while the polymeric solution is fed through the system from the rotating vessel. Upon reaching critical thresholds of rotational speeds and centrifugal forces, the liquid is forced through the orifices in the vessel, extruding long continuous fibrous structures as a result of solvent evaporation and sufficient jet elongation at the orifices.

3.3.2 Governing Parameters of Pressurised Gyration

Like with ES and centrifugal spinning, both physical liquid properties and process parameters must be optimised to achieve successful fiber formation. By altering parameters such polymer viscosity, rotational speed and gas pressure, the collated fibers can be fine-tuned with regards to morphology and size (**Figure 4c**) [344]. Mahalingam et al have developed a mathematical model which interrelates the solution viscosity and surface tension with rotational speed and working gas pressure [345].

3.3.2.1 Process Parameters

Introduction of a pressurised gas once the optimal rotational speed is achieved is required to fabricate fibers of specific morphology and size. If sufficient rotational speeds are not reached, the employment of the pressurised gas will lead to solvent evaporation via the pores in the vessel due to differences in surface tension between the solvent and the polymer [346]. This effect is seen particularly at higher pressures where a greater loss of solvent can be observed. A difference in pressures within the system will encourage solution extrusion through the pores, contributing to the elongation and stretching of the viscoelastic formulation. Therefore, there is a distinct relationship between the pressure of the gas and the resulting fiber size/diameter. Research has found that by increasing working gas pressure, fibers with thinner diameters can be collected. For example. Mahalingam and Edirisinghe found that by increasing gas pressure from $1x10^5$ Pa to $3x10^5$ Pa; fiber diameter reduced from 970 nm to 141 nm following the spinning of 21% wt poly (ethylene glycol) (PEO) [340]. Maximum pressures of 0.3 MPa are typically used with this process [347].

Centrifugal forces in any system are directly proportional to the speed at which the vessel is rotating at. Increasing the rotational speed allows the viscoelastic jet to be stretched via centrifugal forces. Additionally, higher speeds enable total solvent evaporation, resulting in dry fibers mostly within the nanometer range [345]. A threshold rotational speed must be reached in order to achieve successful fiber formation. Low speeds do not yield fibers as the centrifugal force experienced at these speeds are insufficient to overcome the surface tension of the polymeric solution, resulting in the lack of the formation of a jet.

The distance between the vessel/spinneret and the collection plate also plays a significant role in the morphology of the resulting extruded fibers. An insufficient distance will result in the lack of successful solvent evaporation; obtaining samples which will contain organic solvent and can subsequently leading to the formation of wet, beaded fibers.

3.3.2.2 Solution Properties

The viscosity of the formulation to be processed (as a result of the molecular weight of the polymer(s) used) can also affect fiber morphology [348]. Very thin fibers (as low as 60 nm) have been fabricated by careful solvent selection [340]. For any polymer that is processed by pressurised gyration, there is a minimum critical concentration which must be met to ensure adequate chain entanglement, fabricating successful fibers [349]. Like with centrifugal spinning the surface tension of the spinning solution must be overcome by the centrifugal forces to allow extrusion of fibers from the orifices in the vessel [350].

4. Applications of Fibrous Structures Fabricated by Emerging Engineering Methods

These emerging fiber fabrication technologies have proven to have a wide array of applications in various different remits. The following section will focus on the application of these engineered fibers in drug delivery, regenerative medicine (including external and internal therapies such as wound dressings and tissue engineering) and theranostics.

Figures 5, 6 and **7** outlines key examples of spun fibers engineered by electrospinning, centrifugal spinning and pressurised gyration, respectively.

4.1 Drug Delivery and Theranostics

4.1.1 Drug Delivery

The use of fibrous structures, specifically in the micro and nano range in drug delivery has been exploited in recent years. Alongside developing ultrathin fibers, a big advantage of using polymeric fibers as drug carriers is the possibility of encapsulating or entrapping poorly soluble active pharmaceutical ingredients (APIs) /materials within a polymeric formulation. Subsequently, the spun polymeric matrix overcomes the limitation of poor solubility. By dissolving a crystalline material or an API in a solvent, it will convert to the amorphous form of the active. By incorporating this in a viscoelastic polymeric solution, the resulting fibers will be able to carry and release the active in amorphous molecular form; usually as fine particles [347]. The success and efficiency of this will depend on the drug carrier selection as the material should allow for high drug loading, effective cellular uptake whilst applying and maintaining sufficient therapeutic drug concentrations. Fibrous structures and/or fibrous mats make exceptional drug delivery systems, enabling increased controlled drug release due to the high surface area to volume ratio of the fibers. The increased surface area of these structures compared to other morphologies (e.g. particles) enables faster solvent evaporation and therefore allowing drug delivery matrices to be produced which have ability to deliver APIs in a controlled fashion (e.g. burst release, sustained release, delayed release) [351].

The emerging techniques discussed here have exploited this advantage due to being able to process a wide range of materials and they have delivered extremely promising results in the drug delivery remit in a range of applications including chemotherapeutics, antibiotic and protein delivery as well as a range of administration routes such as nasal, transdermal, buccal, ocular and vaginal. **Table 2** highlights some of the key applications of these emerging techniques in drug delivery.

4.1.1.1 Electrospinning

The ES process has shown immense potential in fabricating fibrous drug delivery systems in recent years; with the technique being used to deliver a wide range of APIs. There seems to be a large focus on specific areas where delivery for timely and targeted action is crucial such as anticancer delivery. Chemotherapeutics such as 5FU [352-358], doxorubicin [356, 359-362], paclitaxel [363-366], cisplatin [367-369] and metformin [370] have been used as model drugs to show the effectiveness of ES in cancer therapy. For example, Ghahreman et al fabricated 5FU-loaded PCL/gelatin fibers which showed by increasing the amount of gelatin in the composition; drug release increased [354]. The anticancer-loaded nanofibers exhibited good cell attachment and proliferation of HT-29 colorectal cancer cells whilst exhibiting controlled drug release. Elsewhere, PCL was also used in combination with chitosan to develop electrospun fibers containing 5FU [357]. The nanofibrous system developed also showed exciting potential in colorectal cancer treatment. In a novel attempt to achieve simultaneous release of 3 anticancer actives, Jouybari et al fabricated tri-layered nanofibers utilising blends of chitosan, poly (vinyl alcohol) (PVA) and PLA [356]. 5FU was incorporated into the chitosan/PVA core while the intermediate layer comprised PLA/chitosan and doxorubicin and paclitaxel were loaded into the outer layer consisting of PLA and chitosan. Over 90% drug loading efficiency was achieved here with all three drugs. 5FU demonstrated the slowest release from the tri-layered fibers owing to encapsulation in the inner core. Compared to single layer nanofibers, the tri-layered fibers showed the highest cell growth inhibition. Enhanced cell viability and cell attachment to MCF-7 breast cancer cells demonstrates the potential of multidrug delivery using one drug delivery system engineered using ES.

The ES process has also found to be advantageous in developing fibrous mats for novel controlled drug delivery systems via an array of administration routes such as buccal [59, 371, 372], nasal [373-375], transdermal [194, 376, 377] and ocular [378-382]. ES has found to have the ability to overcome limitations of conventional drug delivery routes of administrations e.g. the transmucosal surfaces that are present in the mouth or the nose.

For example, Kamble et al developed electrospun PVA fibers to overcome the poor water solubility of albendazole, a broad spectrum benzimidazole anthelmintic [383]. The resulting fibers intended for oromucosal administration demonstrated a 5-fold improvement in the dissolution rate of the drug compared to raw drug with *ex vivo* permeation studies showing a 3.2-fold improvement. Similarly, Nazeri et al developed buccal films loaded with indomethacin which demonstrated controlled release of the active and sustained permeation using a porcine buccal model [371]. It was thought that the hydrophobic nature of cellulose excipients used to fabricate the film helped hinder fast release of the drug and enhanced permeation.

Mehta et al demonstrated the use of electrospun fibers as coatings in a novel application for drug delivery via contact lenses [189, 384, 385]. In the first study of its kind, in an attempt to increase and enhance permeation of antiglaucoma drug timolol maleate in the eye, borneol, PVP and poly (N-isopropyl acrylamide) (PNIPAM) were used [384]. The resulting fibrous coatings showed an increase in drug release; up to 20% more timolol maleate was released from the coatings compared to

permeation enhancer-free coatings. More recently, coaxial fibers containing acetazolamide were fabricated to create a novel biodegradable polymeric ocular implant [378]. The PCL based implants exhibited sustained release of the drug following coating of poly (ethylene-co-vinyl acetate), engineering an innovative implant advantageous over existing ocular drug delivery systems.

A running theme with utilising ES to fabricate drug loaded structures which are able to control drug release. Yousefi et al developed core/shall fibrous mats comprising PCL and chitosan as a carrier for statin rosuvastatin [224]. By employing the developed configuration of two concentrically arranged needles, two layered fibers capable of controlling the delivery of the statin were produced. The pH-responsive nature and the hydrophilicity of chitosan (the shell) enabled controlled delivery of the drug.

One major advantage of the ES process is its ability to encapsulate multiple drugs in a single step process for synergistic therapy [225, 386-391]. A recent key example of this is demonstrated by Wulf et al who developed smart-releasing non-woven nanofibers which successfully encapsulated and subsequently released the cytostatic drug paclitaxel and growth factor human vascular epithelial growth factor (VEGF) in an attempt to overcome common complications seen with restenosis [386]. By utilising ES, it was found three times more drug was released after 70 days compared to drug-loaded films produced using spray coatings. Another fascinating study showed the engineering of thermo-responsive drug-loaded fibers for cancer treatment [388]. The resulting “smart” magnetic fibers had the ability to generate heat whilst being able to switch this property on or off, i.e. “on/off switchable heating ability”; showing the two-stage drug release approach here had a more advantageous synergistic effect compared to conventional chemotherapeutic methods.

4.1.1.2 Centrifugal Spinning

Despite the concept of centrifugal spinning showing the process would have great potential in developing effective drug dosage forms, the specific process parameters and spinneret designs has hindered such efforts. Regardless, some efforts have been made to control and sustain drug release from the spun fibers.

In a bid increase the solubility and oral bioavailability of antipsychotic agent olanzapine and NSAID piroxicam, Marano et al utilised solvent-free centrifugal spinning to fabricate drug-loaded sucrose fibers [392]. Thermal analysis and X-Ray diffraction analysis of the resulting structures determined the drugs were in amorphous form; highlighted by the presence of a single glass transition temperature (T_g), exothermic crystallisation and endothermic melting peaks in differential scanning calorimetric thermograms. The drug-loaded fibers showed enhanced dissolution performance compared to the pure crystalline forms of the drugs which can be accredited to the sucrose carrier.

The process of centrifugal spinning enables the production of fibrous structures capable of displaying controlled drug release. For example, Wang et al exploited the high surface area to volume characteristics of nanofibers and yielded PVP fibers loaded with tetracycline hydrochloride [278]. Upon process optimisation, it was possible to engineer aligned fibrous mats that were advantageous in achieving controlled sustained release of the antibiotic. Tetracycline hydrochloride has also been loaded into PCL/PVP fibers, yielding structures with an average fiber diameter of 927 nm and demonstrating a slow-release profile [393]. 74% of drug was released within 24 hours owing to the hydrophobicity of PCL. The blended fibers demonstrated good antimicrobial activity against pathogenic bacteria which is commonly found in dermal infections.

Centrifugal spinning also been used to fabricate microfibers which were subsequently compressed into orodispersible tablets [394]. The dissolution of poorly water-soluble drug carvedilol was significantly enhanced compared to tablets comprising physical mixture of hydroxypropyl cellulose and raw drug. The increased dissolution was attributed to the now amorphous state of the beta-blocker following centrifugal spinning processing. Elsewhere, Wang et al utilised centrifugal melt spinning and found it to be an excellent method for fabricating highly aligned fibers with high drug loading and the ability to modulate drug release [395].

One of the latest studies utilised Forcespinning™ to engineer doxorubicin-loaded pH-responsive composite fibers [282]. The PCL fibers were functionalised with carbon nano-onions and 99% drug release was observed over 15 days; demonstrating the centrifugal spun fibers were capable of releasing doxorubicin in a sustained manner. It is thought the non-covalent bonding to the functional carbon nano-onions led to the sustained release of the anticancer active.

4.1.1.3 Pressurised Gyration

The delivery of drugs via various routes of administration are often met by the challenges such as short residence times or inability to allow penetration of biomacromolecules such as proteins and peptides. The use of nanofibers in these applications has shown to overcome these limitations. For example, research into utilising pressurised gyration to develop mucoadhesive fibers specifically for vaginal drug therapy has been presented [396-398]. A research group in UCL, London has focused on fabricated drug-loaded gyrospun fibers to help aid drug delivery across mucosal barriers found in the vaginal cavity [396]. Using PEO as a carrier polymer, the mucoadhesive properties of various polymer blends was assessed. Fibers as small as 100 nm were fabricated with texture analysis and atomic force spectroscopic analysis showing carboxymethylcellulose (CMC) combined with PEO showed advantageous mucoadhesion with mucin; a simulated vaginal fluid, highlighting the potential of gyrospun nanofibers in vaginal drug therapy. In an extended but separate study to this, the loading and release of progesterone into CMC/PEO mucoadhesive fibers was assessed [398]. The loading of the drug into the fiber resulted in a change in fiber morphology and size, increasing the average diameter. The release of progesterone from the spun fibers was compared to the release of the active from a commercially available pessary. The drug-loaded fibers showed more drug was released compared to Cyclogest, with release happening over a period of 4 hours; reaching 19 %. More recently, progesterone loaded PLA scaffolds were fabricated for intra-vaginal therapy using both ES and pressurised gyration; with the latter engineering patches with superior tensile strength and production yield compared to ES. However, the ES process found to yield much thinner fibers (between average of 6.06 µm and 7.893 µm) [399].

Ahmed et al compared the ES process with pressurised gyration for the delivery of poorly soluble antifungal agents; spinning 4 different polymers; PVP, PNIPAM, polyvinylidene fluoride (PVDF) and poly methyl methacrylate (PMMA) [400]. They found that depending the on polymer used and the method used, the average fiber diameter differed. PVDF and PMMA gyrospun fibers demonstrated smaller diameters with gyrospun PNIPAM fibers showing the largest fibers compared to their respective electrospun fibers. PVP was chosen as the optimal polymer and were loaded with antifungal agents amphotericin B (AMB) and itraconazole (ITZ). Electrospun and gyrospun AMB-loaded PVP fibers exhibited average fiber diameter of 0.88±0.35 µm and 1.78 ± 0.81 µm respectively, whilst electrospun and gyrospun ITZ-loaded PVP fibers showed diameters of 0.94 ± 0.34 µm and 1.60 ± 0.87 µm, respectively. Both methods of fabrication yielded fibers that showed successful release of the

APIs; with burst release of drug observed in the first 15 mins with electrospun fibers. The fibers fabricating using pressurised gyration showed burst dissolution and release after a period of 5 mins; releasing 100% of drug after 60 mins.

PVP has also been used to fabricate amorphous solid dispersion fibers to enhance the dissolution of ibuprofen [401]. The *in vitro* dissolution profile of the three pressurised gyration fibers under sink conditions at pH 1 was between 98.4% - 100.2% of the theoretical values whilst the raw material was approximately 80%. It took 8, 14 and 16 minutes for 50% release from the ibuprofen K90F 10%, 30% and 50% gyrospun fibers, whereas it took 40 mins for the dissolution of 50% of raw ibuprofen under sink conditions. The *in vitro* dissolution profile under non-sink conditions at pH 1.0 was also higher for all three gyrospun fibers than the ibuprofen alone. Using ibuprofen-K90F 10% to engineer fibers resulted in the formation of a supersaturated solution. PVP retards the crystallisation of the API in a supersaturated solution and this characteristic increases with an increase in polymer concentration [402, 403]. The increase in drug content resulted in an increase in solution viscosity and therefore has a direct impact on fiber diameter.

4.1.2 Theranostics

Using complex nano-systems for therapeutic diagnostics, namely theranostics, has become increasingly common in recent years [47, 404-407]. Whilst there are many advantages to current polymeric biomedical implants, they do not possess the ability to provide sufficient contrasting for imaging and theranostics. These limitations have been overcome by incorporating contrasting agents or markers into electrospun fibrous matrices [220]. By incorporating magnetic complexations or actives, the resulting fibrous systems can be spatiotemporally controlled via a magnetic field which is operated externally [408]. This approach has already shown promise in the treatment and diagnosis of various cancers [409-411], resulting in the active development of magneto-responsive devices.

For example, Ramachandran et al developed electrospun fibers loaded with temozolomide for treatment of orthotopic brain tumours [410]. By incorporating iron-doped calcium phosphate nanoparticles, the PLGA-PLA-PCL implants were clearly visible in magnetic resonance imaging (MRI) scans, highlighting successful conferring of MRI contrasting to the nanofiber implants.

Coaxial electrospinning configuration have also been utilised to enable simultaneous encapsulation of therapeutic and diagnostic agents [412]. Eudragit S100 shell and PEO core fibers loaded with API indomethacin and contrasting agent (Gd (III) diethylenetriaminepentaacetate hydrate) were fabricated. The resulting fibers demonstrated targeted release of the NSAID while showing the function of the contrast agent had not been lost or diminished, enabling a platform for delivering both therapeutic and diagnostic agents to the colon.

More recently, coaxially arranged processing needles were used to yield electrospun core-shell fibrous structures for MRI of the intestines [413]. Darwesh et al utilised Eudragit S100 and PVP loaded with gadodiamide to develop orally administrated imaging nanofibers capable of achieving various release profiles at different pH. At neutral pH (7.4), the coaxial nanofibers showed burst release whilst at pH 1.2; release was found to be slower indicating a prospective theranostic device for oral administration of the contrasting agent.

With the use of fibers in theranostics being a recent breakthrough field in the pharmaceutical industry, the lack of research in this area is evident due to the small number of published articles in literature.

Employing ES for this application has shown some promise; however, the use of centrifugal spinning and pressurised gyration for this application is still yet to be exploited.

4.2 Regenerative Medicine

4.2.1 Wound Healing

The skin is the body's largest organ and has multifaceted functions including protecting internal systems from foreign bodies and harsh conditions of the external environment. The skins' ability to provide functions including thermoregulation to immunological surveillance to mechanical barrier functions is a testament to the composition and structure of the skin, more specifically the epidermis [414]. Treatments for any disruption to the natural barrier of the skin typically utilises wound plasters or dressings to prevent any further trauma and to expedite skin regeneration at the site of trauma [415, 416].

The advantages of nanofibers (e.g. high surface area: volume, increased porosity) combined with the fact that various properties of the fibers can be fine-tuned using the technologies discussed here; leads to them emerging as promising engineering method to fabricate wound dressings to help and aid efficient wound healing [417, 418]. **Table 2** highlights some of the key applications of these emerging techniques in both external and internal therapy i.e. API-loaded wound dressings.

4.2.1.1 Electrospinning

Contardi et al attempted to overcome the rapidly dissolving nature of PVP by fibers functionalised with hydroxycinnamic acid derivatives [419]. Due to the high solubility of PVP and high surface to volume ratio of fibers, PVP fibers are limited in providing sustained drug delivery. Ethanolic solutions containing PVP, p-coumaric acid and ferulic acid were electrospun into fibrous hydrogel mats and subsequently thermally annealed. The authors found that the mats showed adequate release of the antioxidants for 8 days; providing a sustained release whilst providing protection to A549 epithelial cells against oxidative stress, demonstrating potential candidates for active wound dressings.

Chitosan is a naturally occurring polysaccharide which has gained particular interest in wound healing. It is thought chitosan accelerates the wound healing procedure by proliferating various structures including inflammatory cells, macrophages and fibroblasts, triggering the inflammatory phase [420, 421]. It also functions as an analgesic and anti-inflammatory agent, providing soothing effects when used with open wounds [422]. For example, the effect of chitosan in supporting the wound healing process has been assessed by developing electrospun PCL membranes [423]. The bioactive wound dressings demonstrated strong antibacterial activity with an increased chitosan concentration inducing faster haemostasis and enhanced re-epithelialisation. Tri-layered nanofibrous wound dressings have also been prepared using chitosan, PCL, and PVA to assess the release of melatonin and the possibility of using this system to accelerate wound healing [424]. Histopathological evaluation showed the epithelial layer had completely regenerated and that there was a reduction in inflammatory cells. Using 20% melatonin, there was also significant reduction in various gene expressions (e.g. TGF-beta 1, COL1A1, and COL31A1). Robiero et al developed wound dressings based on chitosan, PEO, cellulose and acacia extract [425]. Using this blend, both antimicrobial and antifungal properties were maintained, showing antimicrobial activity against an array of microorganisms.

Multi-layered fibers have also been engineered using chitosan, PEO and PCL to attempt to achieve controlled release of lidocaine hydrochloride and curcumin [387]. Both drugs were found to have different release profiles with a rapid release of lidocaine hydrochloride providing immediate analgesic effects while sustained release of curcumin provided elongated antibacterial effects, advantageous in the wound healing process. Elsewhere, curcumin was also loaded into electrospun PVP-based dressings which found to aid complete wound healing without scarring within 20 days [426]. The curcumin-loaded dressings also showed good antimicrobial activity against both *Escherichia coli* and *Staphylococcus aureus.* Alavarse et al also found good antibacterial activity against these bacteria when developing tetracycline hydrochloride-loaded polymeric mats [427]. The electrospun fibers demonstrated a burst release of drug within 2 hours; highlighting the potential for such drug delivery system as a viable candidate for antibacterial-loaded dressings for wound healing.

4.2.1.2 Centrifugal Spinning

As mentioned earlier, the cationic nature of chitosan makes it a suitable candidate in wound healing due to its antimicrobial affects. However, it is most commonly used as a hydrogel in wound dressings or in wound healing. Chitosan-based fibrous mats loaded with cinnamaldehyde or silver showed enhanced antibacterial performance against *S. aureus* [428]. Cell viability tests also demonstrated successful results highlighting the fibrous mats here could be employed in wound healing, providing antimicrobial activity whilst promoting cell attachment. More recently, a water-soluble derivative of chitosan, carboxymethyl chitosan was blended with PEO to fabricate nonwoven mats as wound dressings [429]. SEM analysis demonstrated monomodal fibers, ranging from 1.91 µm to 3.22 µm in diameter. The antimicrobial effects of the carboxymethyl cellulose found to be more prominent with gram positive bacteria than gram negative bacteria due to two different mechanisms of action.

In the last few decades, bacterial cellulose has shown its advantages in wound healing. It boasts excellent mechanical properties and water absorption abilities. Despite this, there are drawbacks in that it is exceedingly difficult to process with conventional fiber fabrication methods, leading to low production yield. Aydogdu et al successfully centrifugally spun PLA/PCL and fabricated an adequate carrier for bacterial cellulose using a blend of these polymers [430]. Scaffolds of exceptional tensile strength and mechanical properties were constructed with fiber diameter ranging from 5.0 µm to 18.5 µm. Utilising a 70:30 PLA/PCL blend, the authors were able to produce bandage-like mats for potential application in wound healing.

Ultrafine fibers have been fabricated, presenting as a good candidate for wound dressings [284]. PLA/gelatin nanofibers (513 -622 nm) loaded with ciproflaxin exhibited a biphasic release profile: an initial burst release of drug followed by sustained release after 1 hour. Antimicrobial activity of the spun fibers showed good performance with effect against *S. aureus* being more prominent than against *E. coli.*

Amalorpava et al., 2013 produced 0.2% tetracycline, 12% w/v PCL and PVP) (with varying concentrations of polymers) fibers by spinning the solution at 2000 rpm via infusion centrifugal spinning [431]. The web of tetracycline loaded fibers generated were used for their antibacterial activity in wound dressings, with the fibers tested against gram positive (*Staphylococcis epidermidis, Bacillus megaterium*) and gram-negative bacteria (*E. coli*, *Pseudomonas aeruginosa*). The drug release from the PCL fibers was slower with only 12.5% of the drug released with 24 hours due to the hydrophobic properties of PCL but the combination of PCL and PVP fibers resulted in the release of 74% of the drug within 24 hours due to the hydrophilic properties of PVP. This results in the formation

of pores with an average pore size of 375 nm which allow for faster release of the drug preventing the bacteria from causing dermal infections and better cell adhesion with PCL providing sustained release to prevent secondary infections making it suitable as a wound dressing.

4.2.1.3 Pressurise Gyration

Wound healing can be seen as an extension of drug delivery; using the fibers to enhance wound healing times whilst providing a drug reservoir within a matrix for sustained drug delivery. One of the biggest advantages of pressurised gyration is the high fiber production rate; enabling the mass production of patches and fibrous mats which are able to house actives for a more sustained action.

The first known application of pressurised gyration in wound healing was by Altun et al in 2018 [432]. Bacterial cellulose was blended with PMMA at various wt%; yielding gyrospun fibers as small as 690 nm. As mentioned earlier, bacterial cellulose is a naturally occurring polymer which possesses durability and exceptional cell compatibility, making it a promising candidate in wound healing. However, when spun alone, fibers are not formed. Blending bacterial cellulose with PMMA enables the optimal liquid properties to be achieved, yielding fibers in the nanometer range; with an average fiber diameter from 1.66 to 6.8 µm. When assessing cell viability using Saos-2 cells, there was no indication of toxicity and by incorporating 5% bacterial cellulose to 50% PMMA, the resulting bandages exhibited enhanced biocompatibility.

Pressurised gyration has also found to be productive in fabricating active-loaded bandages for wound healing. For example, PCL fibers loaded with raw cinnamon were engineered and presented adequate antifungal properties [433]. When exposed to *Candida albicans*, the fungus failed to survive after 48 hours of "treatment". 3 weeks following treatment, no regrowth of the fungus was observed, showing the efficacy of cinnamon as an antifungal agent when processed with pressurised gyration and how the effect of the pure active was not temporary; an outcome that was observed with pure cinnamon powder. This study could be used to promote the use of raw/natural materials in wound healing and wound care.

Loading actives which can aid proliferation of cells to accelerate wound healing has become a point of interest with pressurised gyration in recent years. Cam et al have loaded pioglitazone hydrochloride (an insulin sensitising agent) into PVP and PVP/PCL fibrous mats to engineer both burst release and sustained released fibrous mats, respectively [434]. When incorporating the thiazolidinedione, fiber diameter decreased with pure 12% PVP fibers having an average diameter of 1532.26 ± 519.19 nm and active-loaded 12% PVP fibers demonstrating an average fiber diameter of 603.24 ± 163.50 nm. Using a blend of PVP and PCL enhanced fiber mat strength and demonstrated increased epidermal regeneration and fibroblast proliferation, providing a promising approach in treating diabetic wounds.

More recently the same research group loaded pioglitazone along with metformin and glibenclamide into PVP/PCL fibrous structures with an aim to accelerate wound healing [435]. By incorporating a triple combination of drugs, epidermal regeneration (i.e. hair follicle growth) was observed within 2 weeks. This alongside increased hydrophilicity and wettability of the resulting scaffolds allowed the development of sustained release matrices with ability to offer high drug bioavailability whilst reducing frequency of dosing.

4.2.2 Tissue Engineering

The loss in function or trauma to tissues and organs and the treatment of this is of great interest in the pharmaceutical and biomedical remit. Utilising fiber fabrication techniques to develop functional

tissues is integral in the field of regenerative medicine in a bid to support tissue repair or even fabricating new tissue and/or organs to restore lost function [436, 437]. The structures required for such applications pose a challenge; they must be able to mimic or provide ideal conditions for ECM development, support cell attachment and growth whilst also possessing adequate tensile strength and have typical nanofiber features (high surface area to volume ratio and high porosity) [438, 439]. All these characteristics in conjunction enable the promotion of cell growth and consequently tissue growth.

ES, centrifugal spinning and pressurised gyration all have the capability to fabricate fine-tuned fibers that possess these features and have already shown great promise in the field of tissue engineering and regenerative in recent years **(Table 2).**

4.2.2.1 Electrospinning

ES has been seen as an excellent approach to successfully regenerate tissues and organs [440]. PCL has shown great potential in tissue engineering when processed by various fiber engineering methods. Its mechanical strength and biocompatibility further help its use in regenerative medicine when being electrically processed. For example, Choi et al developed electrospun PCL-based scaffolds embedded with decellularized bone extracellular matrix which found to be a useful biomedical device in bone tissue regeneration showing increased effects on osteogenic differentiation [32]. PCL has also been combined with various polymers to create blended fibrous scaffolds with enhanced mechanical properties and cell attachment capabilities. Akbarzadeh et al fabricated a biphasic fibrous matrix composed of PCL, PVA and gelatin which demonstrated fibroblast interaction and enhanced cell proliferation within 24 hours [441] whilst Ghasemkhah et al developed gelatin/PCL scaffolds which proved to be promising protein delivery systems to aid in the tissue regeneration process [442].

ES has also been used to successfully aid neural regeneration. Hu et al developed scaffolds comprising PCL/gelatin nanofibers functionalised by multi-walled carbon nanotubes [443]. The conductive nature of the scaffolds found to significantly improve their ability to promote Schwann cells differentiation hence showing a promising platform for peripheral nerve tissue engineering.

The fibrous matrices that are engineered by ES using optimised materials also show advantages in post-operative complications in reducing inflammation whilst promoting cell proliferation and tissue growth. For example, gelatin methacryloyl/PCL methacrylated fibers were fabricated for potential use in abdominal hernia repair [444]. The engineered fibers found to vary in mechanical strength in tune with varying the blend ratio. *In vivo* biocompatibility tests showed the absence of necrosis whilst showing good biodegradation and less inflammation.

Use of electrospun fibrous scaffolds have extended into cardiovascular grafts for surgical intervention of injured arteries. PCL tubular scaffolds have been developed that have the ability to mimic both the structure and the biomechanics of blood vessels. Dimopoulous et al fabricated biodegradable scaffolds which promoted cell infiltration and possessed excellent mechanical properties mirroring those of natural vessels [445]. PCL was also used in conjunction with fibrin to develop electrospun vascular grafts which also found to improve cell infiltration and proliferation [446]. The function of the tubular grafts found to mimic the characteristics of native arteries, showing potential in an innovative vessel scaffold for long term implantation.

4.2.2.2 Centrifugal Spinning

The use of centrifugal spinning in tissue engineering research has increased in recent years. Applications in various remits within the field of tissue engineering include bone regeneration, vascular regeneration, nerve engineering and tendon healing and repair.

Natural materials collagen and elastin were combined with PU, a biocompatible synthetic polymer and centrifugally spun at 18,000 rpm [447]. This optimised rotational speed yielded smooth surfaced, non-beaded fibers with enhanced thermal stability. Combining the two natural components found in blood vessels with a polymeric carrier like PU enabled the engineering of tubular scaffolds for suitable vascular regeneration implants.

Padilla-Gainza et al have demonstrated the potential for Forcespinning™ in fabricating nonwoven mats for scaffolds in tissue engineering [292, 448]. Poly (d, l – lactic acid (PDLLA) fibers exhibited homogeneity and narrow fiber size distributions, providing a platform for PDLLA application in tissue engineering [448].

Centrifugal spinning has also benefitted vascular regeneration, more specifically heart valve tissue engineering. Blending PCL and gelatin yielded centrifugally spun aligned fibers which were then embedded in methacrylated hydrogels to produce fiber enforced hydrogels [449]. The authors found that combining fibers with hydrogels yielded constructs capable of mimicking the mechanical stresses of heart values whilst promoting cell attachment and proliferation.

Elsewhere platelet-functionalised 3D scaffolds were fabricated to assess the potential for bone tissue engineering; more specifically the osteogenic potential with human mesenchymal stem cells [450]. Compared to needleless ES, the centrifugally spun matrices demonstrated higher cell proliferation with functionalised platelets of the scaffold successfully triggering an increase in alkaline phosphate, an osteogenic marker. The comparison study demonstrated the crucial advantages of both manufacturing methods and specific targeted immobilisation of growth factors. The same research group prepared a 3D scaffold with osteogenic supplements, yielding fibers capable of releasing drug (doxorubicin) over 30 days [288]. The sustained dug release profile along with its osteoconductive properties makes this scaffold an ideal candidate for cement free bone implants.

Biphasic Janus nanofibrous scaffolds created using centrifugal spinning was first studied in 2017. Khang et al engineered constructs which could provide structural support and enhanced biological activity to the vast remit of tissue engineering [451]. The Janus fibrous networks demonstrated biphasic characteristics with respect to cell attachment. The authors found by altering process parameters, the biphasic characteristics decreased whilst still showing great potential in regenerative medicine.

4.2.2.3 Pressurised Gyration

One of the first studies on record to highlight the application of pressurised gyration in tissue engineering utilised the sister process of pressurised melt gyration. This process eliminated the need of a solvent and instead uses a viscous melt of the polymer. Xu et al assessed the antibacterial properties of gyrospun PCL fibers loaded with silver nanoparticles [452]. Utilising rotational speeds of 36,000 rpm, a working gas pressure of 0.3 MPa and 0.5 mm orifice diameter, the release of silver was scrutinised. The release profile of the silver ions from the fibrous scaffolds was higher from fibers processed at elevated temperatures, with 63 mg L^{-1} of silver ions released within 0.5 hours and 90 mg L^{-1} over a 240-hour period for fibers at processed at 95^{o}C. Whereas, fibers processed at 125 ^{o}C, 155 ^{o}C

and 200°C all released 65 mg L^{-1} of silver ions at 0.5 hours and 96 mg L^{-1},120 mg L^{-1},120 mg L^{-1} by 240 hours, respectively. The antibacterial activity of the silver-coated PCL scaffolds was tested against two gram-negative bacteria *(E. coli* and *P. aeruginosa*) in a Tryptic Soy Broth (TSB). All PCL-silver fibers were equally effective against *E. coli* irrespective of the processing temperature selected, whereas against *P.aeruginosa,* fibers processed at 95°C and 125°C were approximately 90% and 80% effective, respectively, in comparison to fibers processed at 155°C and 200°C which were approximately 60% effective.

PCL was also used in conjunction with montmorillonite nanoclay and nanohydroxyapatite clay to fabricate novel composite fibers for bone tissue engineering [453]. The resulting 3D scaffolds enhanced both cell viability and osteogenic differentiation whilst increasing ECM formation. Increased fiber size was observed upon increasing nanoclay concentration alongside an increase in pore formation. Increasing montmorillonite concentration and increasing the gas pressure (from 0 to 0.3 MPa) also increased fiber diameters. Utilising a pressure of 0.3 MPa and 5 w/w% montmorillonite yielded fibers 2.01 ± 1.38 µm in diameter whilst a pressure-less system at the same clay concentration yielded larger fibers (3.21 ± 2.57 µm).

Gultekinoglu et al employed the use of bioelastomer poly (glycerol sebacate) (PGS) and PVA to synthesise PGS/PVA fibers [454]. By blending PGS with PVA, they were able to overcome the solubility and processing challenges of PGS. The resulting gyrospun fibers were subsequently washed; removing the blended PVA content, yielding pure PGS fibers. SEM analysis determined the resulting fibers possessed a flat morphology due to PVA removal and use of water (thermal crosslinking). The biocompatibility and cell viability of the fabricated PGS fibers was assessed and found the gyrospun fibers exhibited superior cell viability without toxicity. Adequate cell proliferation and cell adhesion highlight the potential of PGS in tissue engineering.

5. Current Challenges and Future Perspective

Nano-sized entities developed by these emerging technologies in particular those with complex release kinetics and multifunctional capabilities, is currently of great interest in the pharmaceutical remit. As discussed earlier, the emergence of nanotechnology has led to significant breakthroughs in the drug delivery and regenerative medicine remit. Technological advances in fiber engineering have made substantial progress in recent years but not without their limitations. Despite the breakthroughs and advances that have been discussed here, many will remain “proof-of-concept” scenarios due to complications regarding biopharmaceutics and *in vivo* responses. Currently, the leading research in electrospinning, centrifugal spinning and pressurised gyration is slowly moving to commercialisation, with some systems already being used in industry (e.g. FibeRio® Technology, NanoSpinner416). Whilst these emerging techniques have shown potential in the fabrication of small, uniform, continuous fibrous structures, the challenge remains of high throughput and large-scale production whilst maintaining the same morphological, chemical, physical and mechanical properties. The multiple processing parameters and liquid properties that need to be optimised to successfully yield nanofibrous structures can hinder the effects of fiber production and lead to complex processing. Despite being able to alter these parameters and develop fibrous structures with tuneable properties, the question or case of process control still remains. Whilst various process/equipment set ups (e.g. coaxial, centrifugal melt spinning, pressurised melt gyration, infusion pressurised gyration) have been

developed to enhance mass production, more research is required to understand the optimisation of the process on a larger industrial scale.

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List of tables and figures

Figure 6. Examples of fibers fabricated using centrifugal spinning. Multi-layered PVP aligned fiber matrices loaded with tetracycline hydrochloride demonstrating mass and controlled fiber fabrication via centrifugal electrospinning a) optical image of aligned fibers and b) SEM image of aligned fibers. Reproduced from [278]. SEM images of Chitosan based composite centrifugally spun fibers loaded with cinnamaldehyde and c) 7% chitosan and d) 9% chitosan for potential wound dressings: reproduced from [428]. PCL-gelatin fibers utilised for heart valve tissue engineering e) SEM image showing fiber surface morphology and f) Digital image of PCL-gelatin fibers collected on the reservoir surface: reproduced from [449]. Fluorescence imaging of g) highly aligned multi-fiber integration using electrospun PVP and polystyrene: reproduced from [29]. h) Tri-material membranes composed of PMMA (grey), PVP (green) and thermoplastic PU (red) highlighting the possibility of engineering highly aligned simultaneous polymeric fiber composite membranes: reproduced from [339]. i) Multidirectional PVP fibers loaded with rhodamine B engineered using centrifugal electrospinning for potential use in biomedical engineering: reproduced from [285].

Figure 7. Examples of fibers fabricated using pressurised gyration. SEM images showing fibers engineering using 5% wt PEO at 36,000 rpm and working gas pressures of a) $1x10^5$ Pa and b) $3x10^5$ Pa: reproduced from [340], SEM images showing gyrospun PEO progesterone-loaded fibers produced using c) 5% wt. progesterone and 15% wt PEO (average fiber diameter 349 nm) and d) 5% wt. progesterone, 13.75% wt. PEO and 1.25% wt CMC (average fiber diameter 404 nm) Reproduced from [398] . SEM images showing a) PGS/PVA fibers following gyration and b) Flattened PGS fibers following PVA removal for uses in tissue engineering. Reproduced from [454].

Table 1. An overview of conventional fiber fabrication techniques with respect to set up, advantages, limitations and applications.

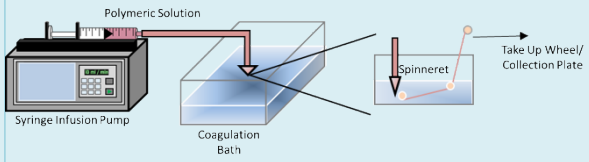
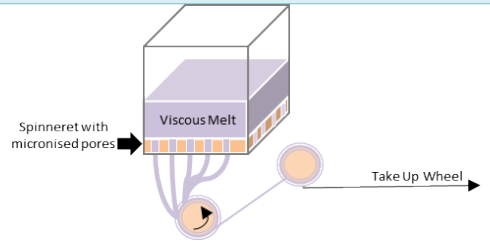
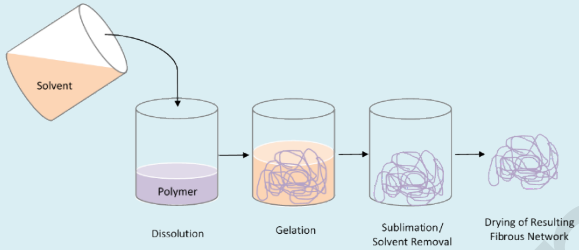
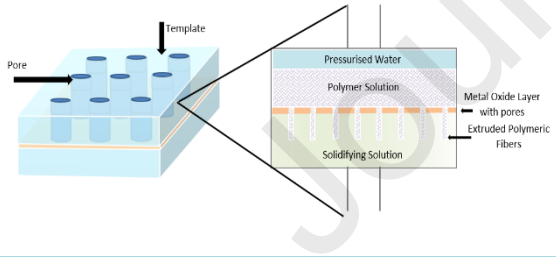
Method	Schematic Diagram of Process Set Up	Advantages	Limitations	Applications	References
Wet Spinning		○ Control fiber diameter ○ Low processing temperatures for temperature sensitive materials ○ Applicable for cell encapsulation	○ Only down to macroscale size ○ Fibers are not aligned ○ Solvent recovery is expensive ○ Low production rate due to viscous drag	Textiles Chemotherapeutics Antibiotic Delivery NSAID Delivery Tissue Engineering Cell Encapsulation	[71-73, 75]
Melt Spinning		○ Can tune structure by altering process parameters and physical solution properties ○ Simple, cost effective ○ High production rate ○ No solvent recovery	○ Only be utilised with materials that melt ○ High solidification rate; poor development of resulting structures ○ High temperatures are used; degradation or denaturation of polymers	Textiles Antibiotic Delivery NSAID Delivery Antifungal Delivery Wound healing Stenting Regenerative Medicine	[100, 108-110, 113]
Phase Separation		○ Minimal equipment, simple ○ Can control pore size and fiber size ○ Can tailor mechanical properties of fiber ○ Creates 3D matrices	○ Not all polymers can undergo phase separation ○ High costs ○ Non-continuous fibers ○ Issues with scale up; small scale production ○ Uses organic solvents ○ Cannot control the orientation of fibers	Implant Development Bone Tissue Engineering	[114, 115, 121, 122, 124]
Template Synthesis		○ Controllable fiber diameter ○ Simple ○ Reproducible	○ Non-Continuous fibers ○ Diameter is determined by pore size ○ Post synthesis process; requires removal template ○ Long; time consuming process with various steps	Drug delivery Scaffolds/Membranes Imaging/Detection	[135]

Table 2. A summary of key selected applications of emerging fiber engineering methods

Method	Application	Polymer	Active	Fiber Diameter	References
Electrospinning	Chemotherapeutics	PCL, Chitosan	5 Fluorouracil	120.2 ± 20.8 nm – 386.1 ± 98.9 nm	[357]
	Chemotherapeutics	PVA, Chitosan, PLA	5 Fluorouracil Doxorubicin Paclitaxel	Up to 485 nm	[356]
	Buccal Drug Delivery	PVP, Methocel™, Tween® 80	Indomethacin	540 ± 400 nm – 810 ± 300 nm	[371]
	Ocular Drug Delivery	PVP, PNIPAM,	Timolol maleate	56 ± 8 nm – 142 ± 35 nm	[384]
	Cardiovascular	PCL, Chitosan	Rosuvastatin	180 nm	[224]
	Antimicrobial Delivery	PCL, Zein, Titanium Dioxide	Erythromycin	625 nm	[223]
	Antimicrobial/ Wound Healing	Chitosan, PEO, Cellulose nanocrystals	Acacia plant extract	80 nm	[425]
	Wound Healing	PVA, Chitosan,	Tetracycline Hydrochloride	119 ± 33 nm	[427]
	Wound Healing	PVA, Chitosan, Starch	--	305 ± 131 nm – 429 ± 138 nm	[422]
	Bone Tissue Engineering	PCL	Decellularised bone extracellular matrix	2.17 ± 0.33 µm	[32]
	Tissue Engineering	PCL, gelatin	BSA	832 ± 221 nm	[442]
	Hernia Tissue Repair	PCL methacrylated Gelatin methacryloyl	--	0.46 ± 0.15 µm	[444]
	Cardiovascular Tissue Engineering	PCL	--	1.16 ± 0.45 µm	[445]
	Bone Tissue Engineering	PDLLA, 4555 Bioglass®	--	100-200 nm	[440]
	Peripheral Nerve Regeneration	PCl, Gelatin, multi-walled carbon nanotubes	--	200 – 900 nm	[443]
Centrifugal	Antipsychotic Delivery	Sucrose	Olanzapine	10.87 µm	[392]

Spinning	NSAID Delivery	Sucrose	Piroxicam	14.10 µm	[392]
	Antibiotic Delivery	PVP	Tetracycline hydrochloride	6 – 19 µm	[278]
	Antibiotic Delivery	PVP, PCL	Tetracycline hydrochloride	927 nm	[393]
	Orodispersible Tablets, beta-blocker delivery	Hydroxypropyl Cellulose	Carvedilol	12.1 ± 3.5 µm	[394]
	NSAID Delivery /Angina and High Blood Pressure treatment	PEG, Eudragit ® EPO, Eudragit ® RL PO, Eudragit ® RS PO, Soluplus ®	Indomethacin Nifedipine	5 - 20 µm	[395]
	Anticancer Delivery	PCL, carbon nano-onions	Doxorubicin	215-353 nm	[282]
	Wound Healing	Chitosan	Cinnamaldehyde	946 -1421 nm	[428]
	Wound Healing	Carboxymethyl Chitosan, PEO	--	1.91– 3.22 µm	[429]
	Wound Healing	PLA, PCL	Bacterial Cellulose	5.0 – 18.5 µm	[430]
	Antimicrobial Delivery/Wound Healing	PLA, gelatin	Ciproflaxin	513 -622 nm	[284]
	Wound healing	PCL, gelatin	--	265 -824 nm	[418]
	Tissue Engineering	PDLLA	--	<1 µm	[448]
	Tissue Engineering	PDLLA PHB	--	1.03 ± 0.69 µm – 1.85 ± 1.1 µm 2.39 ± 0.74 µm – 2.50 ± 0.87 µm	[292]
	Heart Valve Engineering	PCL, gelatin	--	0.64 ± 0.04 µm	[449]
	Bone Tissue Engineering	PCL	Platelets	572 ± 330 nm	[450]
	Tissue Engineering	PCL, Gelatin	--	400 – 800 nm	[451]
Pressurised Gyration	Antifungal Delivery	PVP	Amphotericin B Itraconazole	1.78 ± 0.811 µm 1.6 ± 0.870 µm	[400]
	NSAID Delivery	PVP	Ibuprofen	1.5 – 1.9 µm	[401]
	Vaginal Drug Delivery	PEO, Sodium CMC, PAA, Sodium alginate	--	161 – 280 nm	[396]
		PEO/CMC	Progesterone	40 -1000 nm (dependent on polymer ratio)	[398]

				349 nm (PEO only) 404 nm (11/1*)	
		PLA	Progesterone	7.57-24.79 µm	[399]
	Antibacterial Delivery/ Tissue Engineering	PCL	Silver	14 – 38 µm	[452]
	Wound Healing	PMMA, Bacterial Cellulose	--	Small as 690 nm	[432]
	Antifungal Delivery/Wound Healing	PCL	Cinnamon	2.3 ± 1.3 µm	[433]
	Wound Healing	PVP PVP/PCL	Pioglitazone	1.532 ± 0. 519 nm	[434]
	Wound Healing	PVP/PCL	Pioglitazone, Metformin, Glibenclamide	821.5 ± 521.9 nm (6/4*) 820.6 ± 376.9 nm (7/3*) 740.4 ± 330.4 nm (8/2*)	[435]
	Bone Tissue Engineering	PCL, montmorillonite clay, nanohydroxyapatite clay.	--	1.34 µm ± 767 nm – 3.24 µm ± 3.68 µm (depending on clay content and process parameters)	[453]
	Tissue Engineering	PGS	--	11.8 ± 2.9 µm	[454]

PCL: Polycaprolactone, PVA: Poly (vinyl alcohol), PLA: Poly (lactic acid), PVP: Polyvinyl pyrrolidone, PNIPAM: Poly (N-isopropylacrylamide), PEO: polyethylene oxide, BSA,: Bovine Serum Albumin, PDDLA: Poly (d, l-lactic acid), PEG: Polyethylene glycol, PHB: Poly 3hydroxybutyrate, CMC: Carboxymethylcellulose, PAA: poly acrylic acid, PMMA: polymethylmethacrylate, PGS: Poly (glycerol sebacate). *ratio of polymer blend

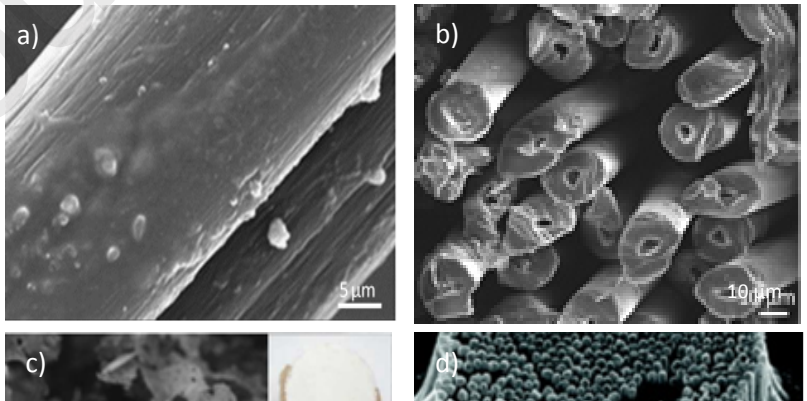


Figure 1. Examples of fibers fabricated using various conventional fiber engineering methods; a) wet spinning; reproduced from [73], b) melt spinning; reproduced from [103], c) phase separation; reproduced from [124] and d) template synthesis; reproduced from [135].

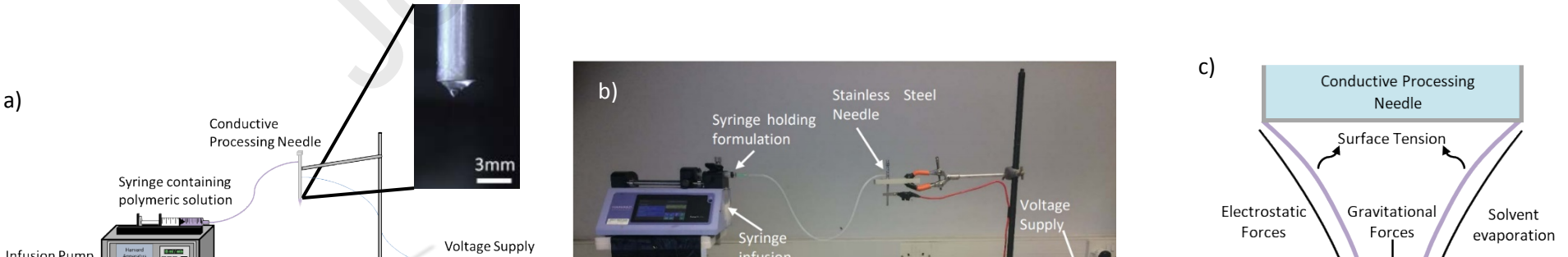


Figure 2. a) A schematic diagram showing the key components of the electrospinning set-up, b) Digital image showing an example of an actual experimental set up of the single needle electrospinning process, and c) A mechanistic diagram highlighting the forces acting on the liquid Taylor Cone at the processing needle exit.

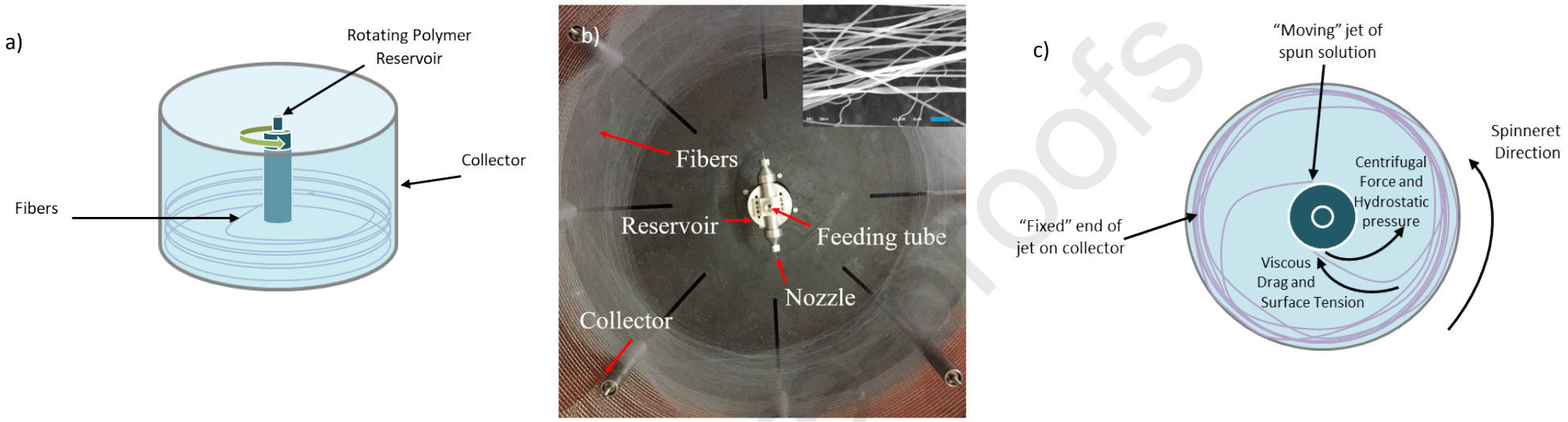


Figure 3. a) A schematic diagram showing the key components of the centrifugal spinning set-up. b) Digital image showing an example of an actual experimental set up of the centrifugal spinning process. Reproduced by [277] and c) A mechanistic diagram highlighting the forces acting in the centrifugal spinning process.

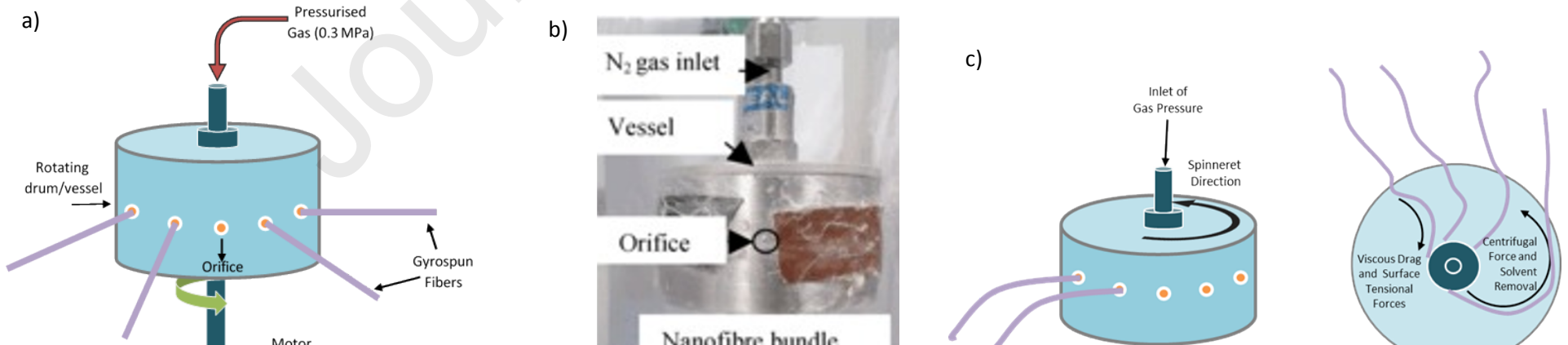
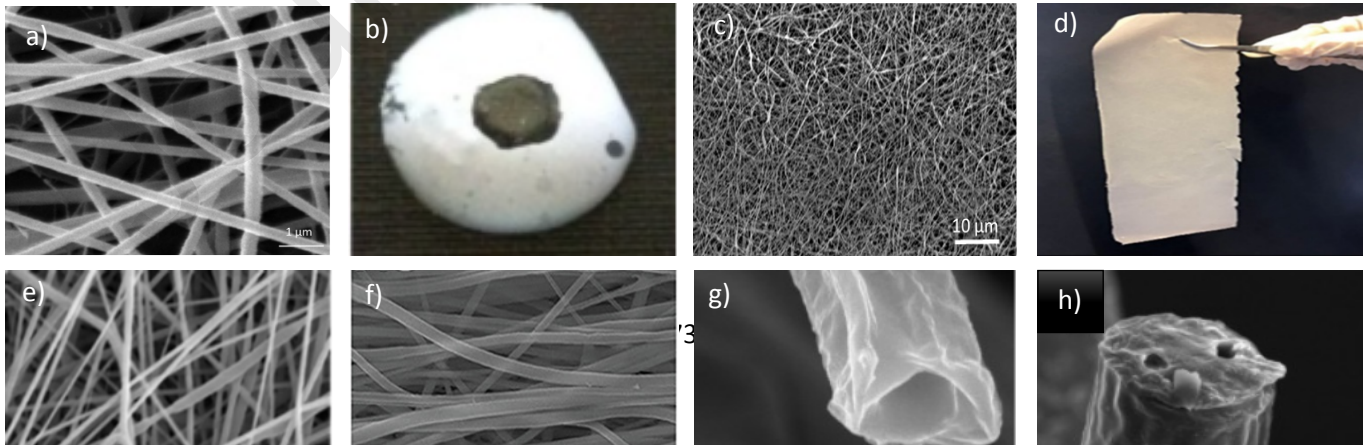


Figure 4. a) A schematic diagram showing the key components of the pressurised gyration set-up. b) Digital image showing actual experimental set up of the pressurised gyration process. Reproduced from [340], and c) A mechanistic diagram highlighting the forces and processes acting in pressurised gyration.



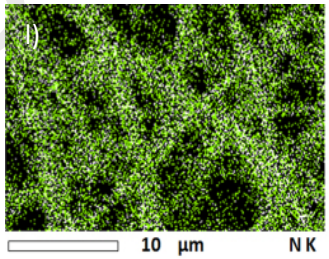


Figure 5. Examples of fibers fabricated using Electrospinning a) SEM images of electrospun tri-layered nanofibers loaded with 5FU, doxorubicin and paclitaxel. Reproduced from [356]. b) Timolol maleate-loaded PVP/PNIPAM electrospun fibrous coatings on contact lenses for the treatment of glaucoma. Reproduced from [384], c) SEM images of electrospun fibrous mats comprising PVA, chitosan and tetracycline hydrochloride for wound dressings. Reproduced from [427], d) Electrospun PEO/Chitosan membrane containing 1% w/v Chitosan for the enhanced antimicrobial activity for wound dressing applications. Reproduced from [425], e) SEM analysis of PCL methacrylated and gelatin methacryolyl (70:30) fibers used in abdominal hernia repair. Reproduced from [444] f) SEM images showing the fabrication of electrospun aligned fibers composed of PCL, gelatin and multi-walled carbon nanotubes. Reproduced from [443]. g) SEM images of core-shell fibers composed of PVP and 5FU (core) and PCL and chitosan (shell), yielding hollowed fibers. Reproduced from [221]. h) SEM image of the cross-section of dual-core graphene-based fibers following immersion in deionised water highlighting the hydrophobicity of the electrically engineered fibers. Reproduced from [455]. i) SEM image of the cross section of coaxially electrospun hollow PVP and PCL fibers for potential use in diffusion tensor imaging and fiber tracing. Reproduced from [231]. j) Electron micrographs of coaxial electrospun fibers comprising PCL and ketoconazole using 1,2-propanediol as a solvent. Reproduced from [232]. k) SEM images of micron-scaled ropes composed of electrically processed PCL utilising a rotating multi-nozzle electrospinning spinneret. Reproduced from [146]. l) Confirmation of uniform distribution of anticancer drug temozolomide within an electrospun PLA-PLGA-PCL wafer for theranostics via brain implants [410].

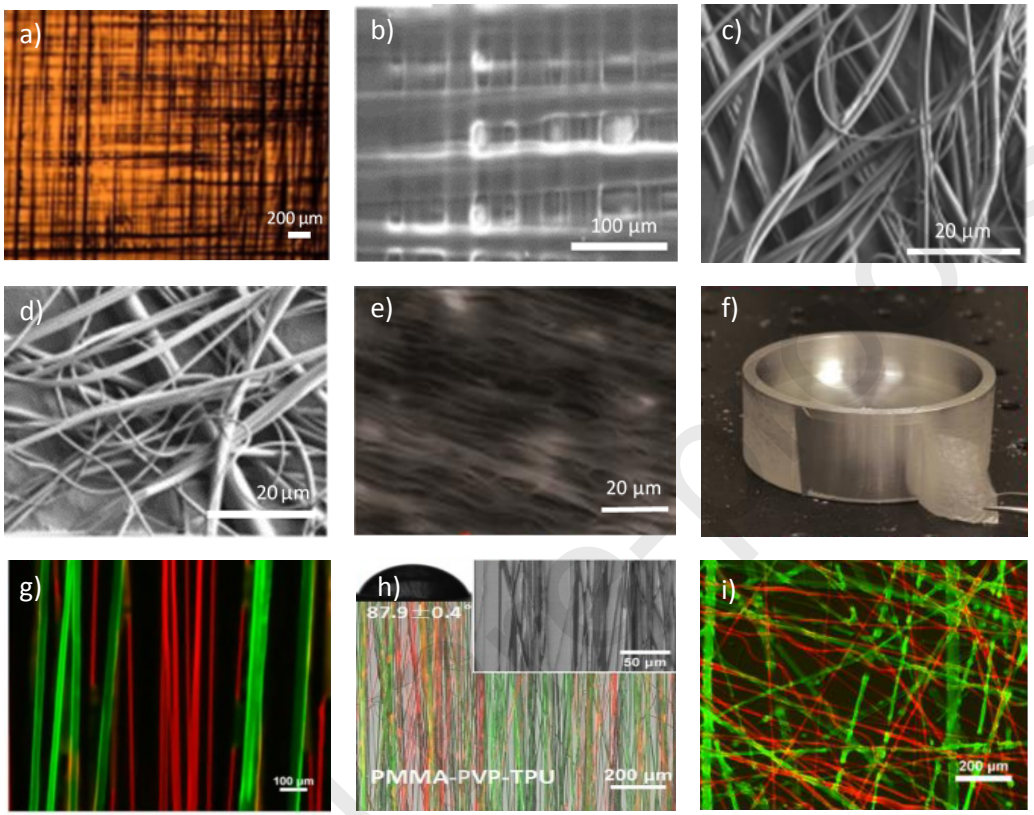


Figure 6. Examples of fibers fabricated using centrifugal spinning. Multi-layered PVP aligned fiber matrices loaded with tetracycline hydrochloride demonstrating mass and controlled fiber fabrication via centrifugal electrospinning a) optical image of aligned fibers and b) SEM image of aligned fibers. Reproduced from [278]. SEM images of chitosan-based composite centrifugally spun fibers loaded with cinnamaldehyde and c) 7% chitosan and d) 9% chitosan for potential wound dressings. Reproduced from [428]. PCL-gelatin fibers utilised for heart valve tissue engineering e) SEM image showing fiber surface morphology and f) Digital image of the PCL-gelatin fibers collected on the reservoir surface. Reproduced from [449]. Fluorescence imaging of g) highly aligned multi-fiber integration using electrospun PVP and polystyrene. Reproduced from [29]. h) Tri-material membranes composed of PMMA (grey), PVP (green) and thermoplastic PU (red) highlighting the possibility of engineering highly aligned simultaneous polymeric fiber composite membranes. Reproduced from [339]. i) Multidirectional PVP fibers loaded with rhodamine B engineered using centrifugal electrospinning for potential use in biomedical engineering. Reproduced from [285].

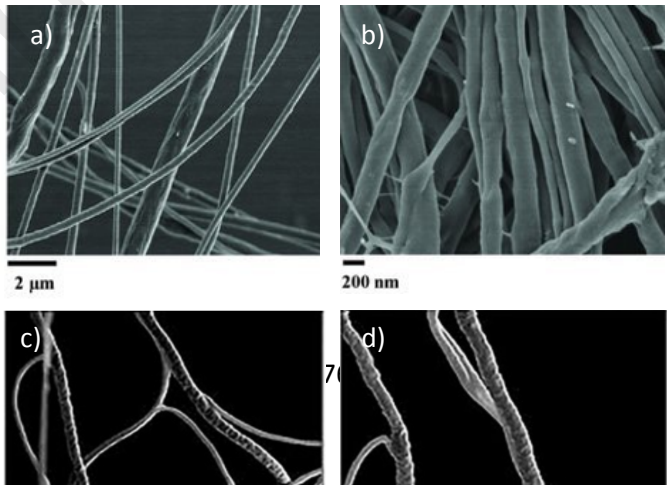


Figure 7. Examples of fibers fabricated using pressurised gyration. SEM images showing fibers engineering using 5% wt PEO at 36,000 rpm and working gas pressures of a) $1x10^5$ Pa and b) $3x10^5$ Pa. Reproduced from [340], SEM images showing gyrospun PEO progesterone-loaded fibers produced using c) 5% wt. progesterone and 15% wt PEO (average fiber diameter 349 nm) and d) 5% wt. progesterone, 13.75% wt. PEO and 1.25% wt CMC (average fiber diameter 404 nm) Reproduced from [398] . SEM images showing e) PGS/PVA fibers following gyration and f) Flattened PGS fibers following PVA removal for uses in tissue engineering. Reproduced from [454].

Graphical Abstract: