Microfluidic manufacture of composite fibres for biomedical applications

Rodrigo Dores[a]; Mónica S.N. Oliveira[b]; Luís Maria Bimbo[a c d]

[a]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, 3000-548 Coimbra, Portugal

[b]James Weir Fluid Laboratory, Department of Mechanical and Aerospace Engineering, University of Strathclyde, 75 Montrose Street, Glasgow, G1 1XJ, UK

[c]CNC – Center for Neuroscience and Cell Biology, Rua Larga, University of Coimbra, 3004-504 Coimbra, Portugal

[d]CIBB – Center for Innovative Biomedicine and Biotechnology, Rua Larga, University of Coimbra, 3004-504 Coimbra, Portugal

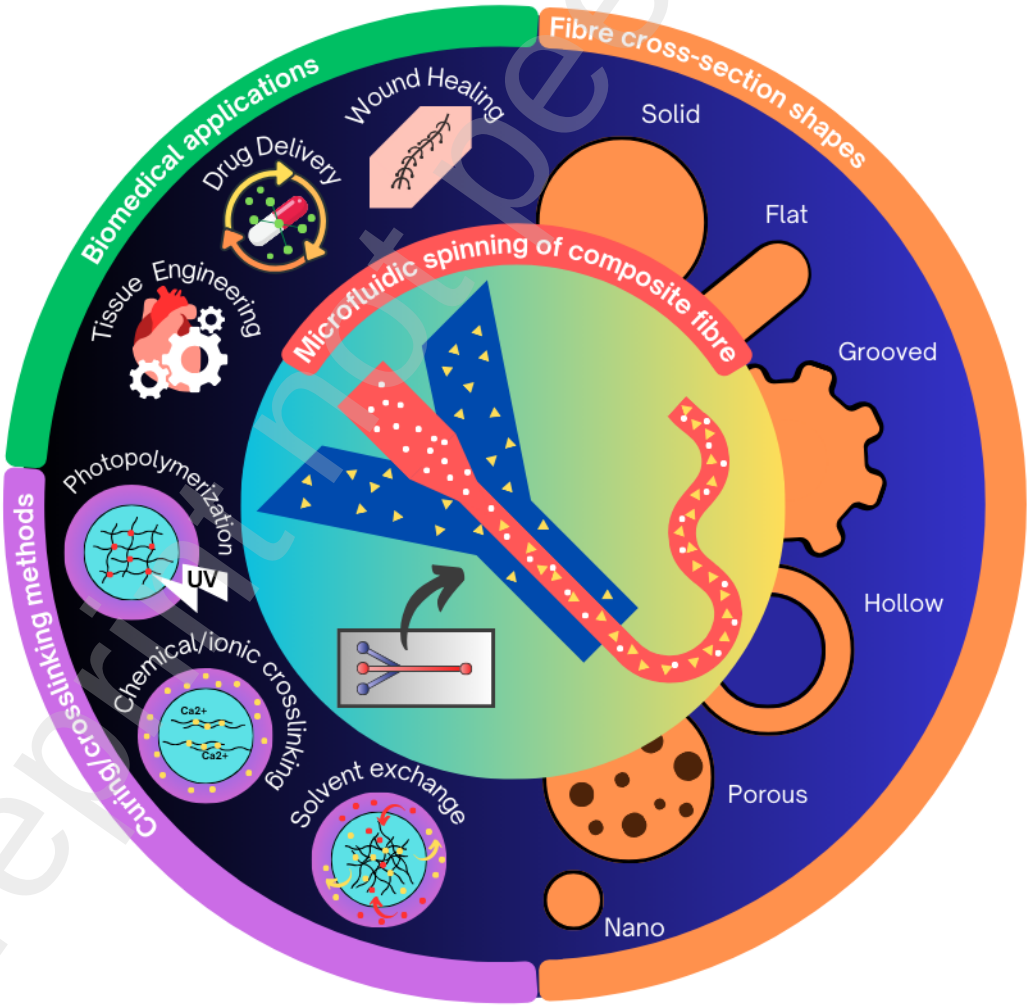
Abstract

Fibrous materials are fundamental building blocks found ubiquitously throughout nature. In order to replicate and harness the unique properties of natural fibres, microfluidic technologies have been employed and refined to allow for a precise control over the mechanical properties, diameter, alignment, and morphology of spun fibres. To further their versatility and adaptability, and to better mimic their natural counterparts, microfluidics technologies have also allowed for the integration of multiple materials and functional components at the microscale giving rise to composite fibres. These fibres, composed of a combination of different materials, offer a wide range of properties and functionalities that surpass those of their individual components and can be tailored to specific applications. This review discusses various microfluidic fabrication methods, including co-flow, multi-channel, and emulsion-based microfluidics, highlighting their advantages and limitations. The review also compares natural and synthetic polymers employed in microfluidic fibre manufacture and examines the influence of process parameters on the properties of composite fibres, such as mechanical strength, porosity, and biocompatibility and discusses the incorporation of nanoparticles, biomolecules, and microstructures within the fibres to tailor their functionalities for specific biomedical applications. Finally, the paper provides an outline of current trends as well as future directions for the field.

Statement of Significance

Microfluidic technologies have emerged as powerful tools which enable the precise handling of small volumes of liquids at the microscale. Due to their ability to miniaturize complex systems, reduce costs, and facilitate high-throughput experimentation, they have been driving advances in chemical synthesis, diagnostics, biotechnology and medicine. Microfluidic platforms are especially well-suited to precisely manipulate polymer materials into fibrous structures with a remarkable degree of control over their composition, structure, and morphology. By harnessing microfluidic control, it is also possible to merge various substances into fibres to form complex, multifunctional composites to further broaden their range of application. This review highlights the microfluidic techniques employed for composite fibre manufacture and illustrates their transformative potential in the biomedical field.

Graphical Abstract



1. Introduction

Fibrous materials are ubiquitous building blocks in nature and industry [1]. Their remarkable versatility and mechanical properties make fibrous materials essential not only in the intricate web of ecological systems but also as integral elements in the construction and production processes across diverse industries and sectors, namely in the textile industry [2], in tissue engineering [3], in sensor electronics [4], in high-performance filtration systems [5], in new energy materials [6–8] and even in civil engineering [9]. Currently, healthcare materials represent a substantial part of the global research endeavour and, consequently, the development of fibre-based technologies and materials also represents a key-subject in the (bio)medical landscape, specifically in the therapy, diagnosis, and monitoring areas [10]. Fibres can be spun from either natural or synthetic polymers, and further woven into complex scaffolds using different approaches. Micro and nanoscaled fibres are more suitable for biomedical purposes, due to their high surface area/volume ratios, favourable interfacial interactions, surface roughness, tuneable surface functionalization and configuration into three-dimensional (3D) heterogeneous structures [1,11]. However, a simultaneously reproducible, precise, tuneable, versatile and large-scale synthesis method for micro/nanofibres is quite cumbersome to achieve using conventional techniques [12], such as melt-spinning [13], electrospinning [14], conventional wet-spinning [15], direct writing [16] and dry-spinning [17].

In the late 20th century miniaturization-tailored concepts, such as micromanufacturing, micro systems technologies, and other analogous, emerged. They involved the production of precision miniaturized components or systems and, due to their size, considerably enhanced material's aspect ratio, precision, and versatility [18]. The rise of microfluidic technology is a clear example of this trend [19]. More recently, this approach was applied to the fabrication of polymer fibres [20] and thus microfluidic spinning technology (MST) emerged as a novel powerful and versatile platform for carefully engineered spinning of fibrous materials. Its unmatched parameter controllability, shape and material versatility and functionalization features are some of the main advantages over traditional spinning methods [21–25]. The development of novel fibres and production methods has become a focal point in biomedical research, due to the increasing demand for high-performance fibres and expansion of its application fields [1] (discussed in section 5.2), as conventional fibres generally fail to present suitable design flexibility and mechanical/functional features for complex applications. In this work we will discuss the potential of microfluidic technology in the context of manufacture of composite fibres for biomedical applications. Firstly, current and conventional production techniques for polymer fibres will be showcased and advantages/limitations summarized. The microfluidic approach to fibre production will focus on basic mechanisms of microfluidics and recent advances on types of microfluidic platforms, and microchannel geometries and cross-sections. Additionally, some

of the most commonly spun polymer materials in MST will be analysed (characteristics and biomedical applications of each). The rationale behind composite fibres is then introduced and, afterward the microfluidic manufacture of these feature-tailored hybrid fibres is described. Several types of fibre shapes, geometries and functional properties are presented with the intent of highlighting the immense versatility of these microfluidic-spun composites. Finally, the most relevant biomedical applications are summarized with practical examples, and future perspectives for this technology are discussed. This particular review focuses majorly on production technology matters of composite fibres, rather than on applied biological/pharmacological mechanisms, thus differing from previous reviews.

2. Fibre production methods

In addition to the processes to naturally produce plant fibres (namely, coconut, straw, or cotton fibres) and animal fibres (such as spider silk, silkworm silk, or collagen), fibre manufacture involves a considerably wide portfolio of techniques, either physical or chemical. Currently, these can be divided into spinning and non-spinning manufacturing techniques. Spinning methods employ external forces to assembly fibres (electric force, centrifugal force, hydrodynamic shaping, gas compression, etc.), conversely to non-spinning techniques. Overall, spinning techniques hold greater academic and industrial interest in the biomedical area, attributable to the high versatility, cost-efficiency, ease of operations, and wide applicability [3,26].

Regarding the fibres' fabrication methods, traditional macro-scale spinning processes include wet-spinning, dry-spinning, melt-spinning, direct drawing, and direct writing (**Fig. 1**). Each spinning technique holds its own characteristic processing mechanisms and parameters, so a technique's suitability clearly depends on the fibre's final applications, desired features and materials [1,27,28]. Conventional **wet-** [29], **dry-** [17], and **dry-jet wet spinning** [30] are classified as solution-based processing spinning techniques as the polymer is spun in solution form. Fundamentally, in these spinning methods, a syringe pump is used to extrude the liquid-state polymer through a spinneret into a collector, which can be then solidified via chemical reaction or solvent evaporation [11,31]. **Melt-spinning**, on the other hand, initially makes use of polymers in pellet form [13]. Melt-spinning is highly desirable for the industrial setting, give it is simply based on the polymers' melting followed by fibre's solidification/drawning, without requiring additional reagents/solvents [2]. Although it is a well-established, straightforward and scalable process, issues related to thermoplasticity evidently restrict the material's choice. **Direct drawing** consists of a self-assembly process at the air-water interface (via molecular interactions or polyelectrolyte complexation), where a filament can be readily drawn from a generally aqueous liquid reservoir [32,33]. Although it is a highly sustainable approach and has been

commonly employed in industrial manufacturing, this method lacks versatility and is unable to fabricate nanoscale and/or functional fibres [28]. Computerized approaches have also emerged in the fibre manufacture space, particularly with computer-designed 3D models' translation into physical substrate (bottom-up manner) [34]. **Direct writing** follows this *modus operandi*, where the "ink" is precisely deposited, enabling the construction of complex "layer-by-layer" structures [16].

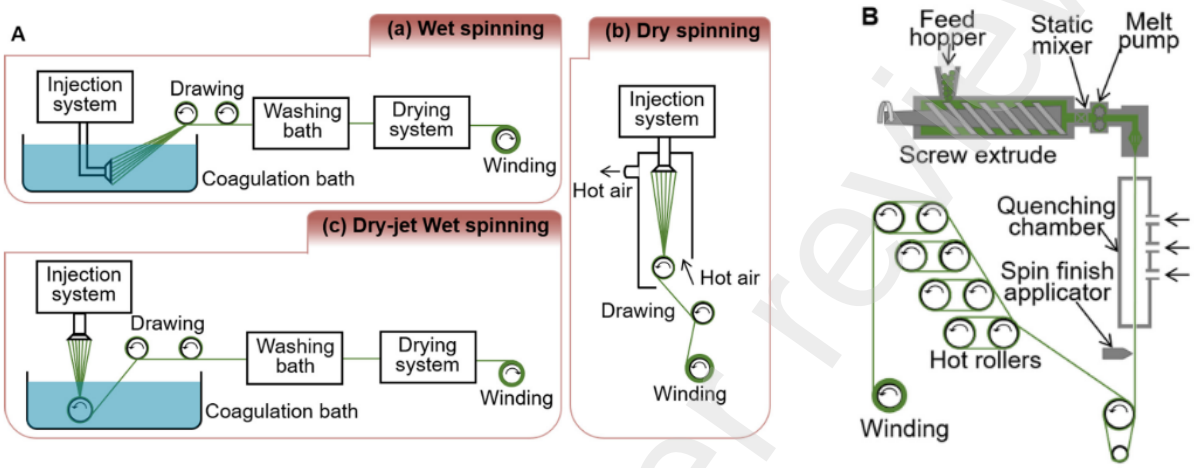


Fig. 1 – Schematic diagrams of common spinning methods. A) wet-spinning (a), dry-spinning (b) and dry-jet wet spinning (c); B) melt-spinning. Reproduced with permission from Li et al. [35] Copyright Elsevier 2023.

Polymer-based fibrous materials can be divided into natural or synthetic, according to their origin [10,36–39], and have already been applied to varied fields such as tissue engineering, sensor electronics, textile industry, and even civil engineering [9]. Nevertheless, polymer fibres' research is (and must be) continuously focused on expanding application areas, development of novel fibre types and materials, and also improvement of synthesis technology beyond the currently established methods. Advancements on high-performance fibres represent a major step into the fulfilment of this technology in tissue engineering [40], biomedicine [41], diagnostics and monitoring sensors [4,42], chemical reactors [43], optical devices [44] and wearable electronics [45].

Electrospinning stood out as a remarkable fabrication method for optimized micro and nanoscaled polymer fibres [26,46–50]. This technique was introduced in the 20th century and relies on electrical forces to create an electrically charged polymer jet. Specifically, a high electrical potential is introduced to a syringe metal needle, inducing an electric charge on the liquid surface. When the applied electrostatic forces reach a critical value, liquid droplets form at the tip of the needle, as repulsive electrical forces overcome the polymer's surface tension, accelerating a charged jet toward a metal collector [51]. A rapid solvent evaporation then takes place, generating thin solid fibres with

tuneable nanoscale diameters, with commendable yields [11]. The micro/nanoscaled fibres obtained in this fashion can be easily optimized by tuning process and solution parameters (for example, electric field strength and polymer concentration, respectively) [52]. Despite continuous advances, electrospun fibres are yet to fully entered the pharmaceutical market due to scaling-up and regulatory issues. Some other techniques have been developed based on the combination/adaptation of established methods, originating methods such as encapsulating dry-jet wet spinning [53], and noticeably "magneto-spinning", which utilizes a permanent magnet (fixed on a rotating device) and a polymer solution containing magnetic nanoparticles [54]. Compared to conventional electrospinning, this method formed fine nanofibres after rotation-based stretching, without employing high voltages.

The aforementioned methods present, nonetheless, several limitations (including the highlighted electrospinning), such as the high pressure, high temperature, high voltage (electrospinning) and/or shear potentially employed in these processes which restrict the choice of raw-materials and the production of functionalized fibres [1,52]. For example, cell-laden polymer fibres are challenging to fabricate using a traditional spinning process due to cellular degradation when subjected to melt-spinning's high temperatures [55,56]. The use of organic solvents is also a critical limitation. Particularly in electrospinning, where the most used polymers are relatively hydrophobic and highly cytotoxic organic solvents/blends [38,57]. Frequently, the solvent's rapid evaporation and interfacial tension are likely to additionally lead to irregularities in the fibre's surface. Also, by utilizing the referred techniques at industrial scale, it is generally difficult to create complex micro/nanoscaled fibres, due to poor control over fibre's morphology, dimension and alignment [58]. The mentioned limitations and barriers to these conventional methods thus limit the therapeutic value of fibres, notably in biomedical areas. Consequently, a demand for innovative production methods for polymer-based fibres is still a currently relevant research subject.

3. Microfluidic approaches for fibre production

3.1. Microfluidic's basic principles and mechanisms

The significant differences in fluid behaviour and chemical reactivity observed at a micro/nanoscale are the basis for microfluidic science. This technology platform represents a highly interdisciplinary scientific branch centred in the manipulation and processing of small fluid volumes (10^{-9}~ 10^{-18} L) [19,27,35]. Such downscaling approach promotes unique fluid phenomena in microfluidic devices' channels (typically ten to several hundred µm), linked to high surface-to-volume ratios which enable rapid heat and mass transfer, generally not possible at macroscale [59]. In microfluidics devices or reactors, viscous forces typically dominate over inertial forces, leading to flows at low Reynolds

number (*Re*), a dimensionless number used to estimate if the flow is laminar or turbulent, representing the ratio of inertial to viscous forces (**Eq. 1**):

$$\mathrm{Re} = \frac{\rho \mathrm{UL}}{\mu} \quad \textbf{(1)}$$

where ρ represents the density of the fluid (kg/m^3), U the average velocity of the fluids (m/s), L the microchannel's length (m), and μ the viscosity of the fluid (Pa·s). Generally, in microfluidic reactors, laminar flow prevails, velocity is constant, and Re is usually kept below 250 [60,61]. Focusing on fluid dynamics, the governing equations are Navier-Stokes equations (**Eq. 2**) and can be simplified by assuming a low Reynolds number, and incompressible and fully-developed (constant parameters) Newtonian fluids [62]:

$$\rho\left(\frac{\partial \bar{\mathbf{u}}}{\partial \mathrm{t}} + \bar{\mathbf{u}} \,.\, \nabla \bar{\mathbf{u}}\right) = -\nabla \mathrm{p} + \mu \nabla^2 \bar{\mathbf{u}} + \bar{\mathbf{f}} \quad \textbf{(2)}$$

where is u the velocity field, is p the pressure field, and f is the force field. In this laminar setting, mixing process takes place only through limited flow interfacial diffusion [27,61]. The thermal Péclet number is another relevant dimensionless number, which characterizes the microfluidic regime, describing the ratio between heat transport due to advective and diffusive transport. In microreactors, the Péclet number is relatively large but generally inferior to 1000. Thus, diffusion-related mixing can be even neglected in most cases. Nonetheless, mixing enhancement can be achieved through increased microchannel's length (using long winding channels, e.g.) [43,59]. Overall, in microfluidic fluid dynamics, flow is determined by surface tension and fluid viscosity [20,63,64].

The microfluidic approach, although a relatively novel technique, has already emerged as a highly advantageous platform for micro and nanoscaled materials' manufacture. Biomimicking spiders' and silkworms' fibre-spinning process, microfluidic spinning technology (MST) emerged as an alternative fibre manufacture platform. Typically a wet-spinning process [65], this method gained significant attention due to its outstanding tunability and flexibility (even with orderly complex structures), high yields, fast and cost-effective production, and suitable scalability, enabling the fabrication/spinning of fibres with diameters ranging from a few micrometres (microfibres) or even nanometres (nanofibres) to several hundreds of micrometres, while utilizing mild spinning environments (normally aqueous), simple apparatus, and an overall uncomplicated workflow [38,60,66–68].

Typically, a microfluidic system is composed of one or more microchannels, sample fluid(s) (polymerizable precursor[s]), and sheath solution(s), composing a "core-sheath" coaxial flow. The outer sheath-like fluid possesses a crucial role in shaping the fibre, morphology and in the solidification process, whilst avoiding inner fluid's contact with the channel's wall and clogging [20,69–72]. The

general workflow for MST is quite uncomplicated and convenient: reagents are loaded into their respective syringes connected to the microreactor's inlets, flow rates are set for each inlet, cross-linking/fibre solidification and product collection are made from the outlet in an exceptionally reproducible manner [73]. The need for manual operation is reduced and, if existent, it usually happens at the beginning and end of the workflow, since the process is programmable and automatic. On the other hand, production on batch-mode reactors (conventional spinning) is usually time-consuming, requires more fabrication steps and can significantly lack control over synthesis parameters, although it is cheaper and has considerably greater scalability, compared to microfluidic spinning [59,74]. A summarized "face off"-like comparison between microfluidic and conventional batch manufacture is presented in **Table 1**.

Table 1 - Comparison between microfluidic reactors and batch reactors. Microfluidic devices depicted characteristics focused on laminar flow-based systems. As a technologic platform for micro and nanoscaled fibre's fabrication, microfluidic systems clearly stand out as highly advantageous. The ability to scale-up remains as an intrinsic limitation to microfluidic approach, due to its small scale, although it can be overcome with parallel scale-up procedures [59].

Factors	Microfluidic Reactors/Devices	(Macroscopic) Batch Reactors
Chip-scale operations	Yes	No
Process Tunability	Very high	Low
Fast reaction	Yes (seconds or less, usually)	No (hours or even days)
Precise control	Yes, precise control over parameters over each step	No (particularly lacking In-Process Control)
Reproducibility	High	Low
Automation/ Programmability	Yes, programmable equipment enables tunable automation	No, usually require watching over the process
Low reagents consumption	Yes (micro/nanoscale)	No
Scalability	Low to Moderate (parallel scale-up)	High (easy manufacture of large quantities)
Low cost	Yes (with scale-up)	Yes (with large scale), otherwise, only moderate
Mild conditions	Yes	No (use of organic solvents, high temperatures, high voltage, etc.)
Usefulness for R&D	Very high (new materials' development and screening)	Low (low efficiency and Unreliable control)

Considering the critical process parameters, this microfluidic approach can be precisely tuned by controlling the flow rates, concentrations, input shapes and structural design of the microchannels.

Also, the optimal solidification process should be fast enough to form fibres but still retain extrusion efficiency. Therefore, viscosity ratio between flows must be carefully controlled, as it impacts fibre solidification [75]. In 2009, a division between microfluidic systems, based on the device's main liquid propulsion principle was recommended. The five categories proposed were: pressure driven, capillary-based, centrifugal, electrokinetic, and acoustic platforms [63]. Amongst these, pressure-driven microfluidic devices are the most desirable for chemical synthesis and thus for fibre production, due to easy control over production parameters and design flexibility. In this review, the described microfluidic devices are pressure-driven reactors, if not stated otherwise. Pressure-driven devices can be further divided in: single-phase laminar flow and multi-phase discrete/segmented flow systems. Single-phase devices display a simple design, fundamentally composed of multiple inlets for different (reagents') flows, flow intersection, and an outlet for the final reaction products. Conversely, in discrete flow devices, flow compartmentalization occurs and includes liquid droplets [76] and gas segments [77], whose formation is based on specific nozzle designs (Y-shaped, T-shaped, or cross-shaped geometries) [59].

Considering each type of microfluidic system and their respective advantages and limitations, the most commonly employed method for fibre production is, clearly, the single-phase flow microfluidic system [61].

Shear-rate-dependent fluid viscosity, innate to non-Newtonian fluids and the most utilized in this setting, is also crucial, although by employing well-designed microfluidic systems, shear stress phenomena can be reduced to minimal due to the characteristic laminar flow's conditions in microfluidic chips [12,58]. Furthermore, the mixing process is greatly improved due to channels' nanoscaled dimensions, resulting in rapid reaction kinetics and high yields, while also providing a far more precise and easy control over fibre's parameters and morphology, under mild reaction conditions [39,60]. The reduced reactor dimensions is another beneficial feature, since it minimises spatial requirements. It was also verified that microfluidic manufacture of cell-laden functionalized (composite) fibres is much more suitable than conventional techniques, since the conventional nozzles and/or harsh conditions used in these techniques were shown to harm cell viability, while a two-inlet microfluidic chip allowed for the preservation of the cells' viability and even its distribution along composite alginate microfibres [58]. A wide range of polymers (and functional biomolecules) is considered suitable for MST, which further optimizes this platform's potential for fibre functionalization and consequently augments its biomedical value [60,78–81].

Overall, microfluidic systems justifiably have extensive advantages compared to other spinning methods, such as: precise controllability of fibre morphology, exceptional design flexibility and

material flexibility, mild conditions, energy-saving, cost-effectiveness, high surface to volume ratio, rapid mass/heat transfer, possibility of continuous production and uncomplicated loading capacity/functionalization [35,82–84]. Unfortunately, these systems have also a generally low production speed compared to conventional techniques, significatively limiting their mass production. However, this drawback isn´t quite as impactful as it may seem, since microfluidic synthesis is the current suitable choice for complex, functional and high-value fibres for specific biomedical purposes (even in smaller amounts). Furthermore, parallel scaling-up has also been successfully employed to scale out composite fibres with homogeneous distribution [61,85]. A comparative analysis between different spinning methods is shown in **Table 2**.

3.2. Microfluidic fibre production: types, platforms, geometries and fibre shapes

The most critical component for microfluidic synthesis is the microchannel [35]. This normally cylindrical or rectangular structure integrates several types of platforms: two-dimensional (2-D) microchips [86], 3D-printed microfluidic microchips [87], capillary-based [88], microfluidic tubular [89], pipet- and needle-based [90,91], and double-syringe injection devices [92]. Currently, these microchannels are commonly made of polydimethylsiloxane (PDMS), Cyclic Olefin Copolymer (COC), poly(methyl-methacrylate) or PMMA, glass, metal and polymers. The two most dominant microfluidic chips to generate polymer (nano)fibres are glass capillary and PDMS chips [12,93]. Glass, used in capillary-based devices, is a low-cost material with favourable applicability based on its surface hydrophilicity, stable coaxial flow generation, possibility of surface coating modifications and diameter control by tempered pulling and cutting processes [94–97]. Regular or pulled glass capillary-based systems are generally uncomplicated, swift and relatively inexpensive, however they are also poorly reproducible and quite burdensome in terms of labour and time [27,98]. Therefore, the industrial production of capillary devices and its applicability appear to be at the time substantially underdeveloped.

Soft lithography processes are also used to fabricate two-dimensional (2D) microfluidic chips. These microchips are usually made of PDMS, but also PMMA, Polytetrafluoroethylene (PTFE), silk and even metals [99]. These systems offer advantages such as precise design/fabrication, high reproducibility, compatibility with most (bio)materials, relatively inexpensive production (although the required cleanroom facilities might entail a considerable initial investment [100]) and good scalability/prototyping. Microchannels with rectangular cross sections are normally constructed with conventional lithography, but recently other approaches are being employed to achieve more complex cross-section design, including cylindrical and grooved channels. Shin et al. proposed a microfluidic device fabrication method which used thin grooved PDMS membranes and bonded them

to a PDMS mould, generating cylindrical channels with well-designed longitudinal grooves, with Norland Optical Adhesive 73 (NOA73) as a moulding auxiliary [75]. This microchannel setup enabled the generation of fibres with well-aligned cell growth on its grooves, which are particularly favourable for anisotropic tissue formation. Plenty publications have by now reported a similar approach and successfully constructed cylindrical and coaxial-flow PDMS channels, with great size and structure versatility [101–103]. Nguyen et al. notably produced the mentioned channel type via replica moulding, using a PMMA substrate and validated the method for hollow fibre manufacture [103].

Alternative techniques have been introduced to optimize time, expenditure and efficiency in prototyping. Pham et al. even developed a simple and straightforward method to fabricate PDMS microfluidic chips/devices in an appreciably cost-effective manner, without the requirement of specialized facilities for soft lithography, using a simple embedded template method. This method, successfully employed in previous works [104], uses plastic tubes and wires to mould a template with PDMS pre-polymer and curing agent on a Petri dish. All the tube and plastic templates were then pulled out from the cured PDMS matrix and exposed to oxygen plasma as a finishing treatment, resulting in PDMS microchannels which were subsequently employed in a facile microfluidic production of hollow fibres [105].

More recently, 3D technology/printing has also emerged in the microfluidic spinning chips' arena [106]. Although conventional glass- and PDMS-based microfluidic devices still possess great potential, they only allow certain structural flows and fibre size due to limited structural features, channel size and fabrication process. Consequently, these devices lack feasibility in complex materials' manufacture. 3D microfluidic chips arose as a solution to form highly heterogeneous fibres [107]. These chips commonly use multiple-layered PDMS microchannels which form coaxial devices, with remarkable value for highly heterogeneous/complex fibre manufacture. PDMS, a commonly utilized material in microfluidic chips, still faces some challenges in a 3D setting, such as its hydrophobicity and the lack of an effective bonding method for PDMS layers, which limit its practical use in 3D chips and, therefore, its accuracy and functionality in the fabrication of more complex fibres [108]. Moreover, with increasingly larger and more complex of coaxial 3D devices, manufacture tends to be more time-consuming, complicated and less yieldable [109]. In order to surmount some of these limitations, some approaches have been proposed. Morimoto et al. tested a modular technique in which 3D printed microfluidic modules were connected via screw threads. The authors concluded the device was viable for complex and versatile fibre production, and, also, the device's modular characteristic allowed for its use as a conventional and a 3D microfluidic device, according to the desired application [109]. Oyama et al also proposed a novel bonding approach to form 3D integrated PDMS microfluidic chips by simply applying γ-ray irradiation to stacked PDMS layers. This process led

to strong covalent bonds, long-lasting hydrophilization and sterilization of internal microchannels, while enhancing mechanical strength of PDMS due to Si–Ox bond radiation-tailored genesis. This method requires no other chemical reagents, does not undermine the PDMS advantages, and demonstrates feasibility in a large-scale production setting [108].

3D printing of microfluidic chips, a trending platform, enables a fast and single-step manufacture of the desired chip, while also being more accessible, cost-effective, and providing a higher versatility to research/production labs, compared to traditional soft lithography and casting methods [106]. Although PDMS presents limited 3D printability, some recent articles have reported promising 3D printed PDMS-based microfluidic chips [110,111]. Additive manufacturing methods, such as novel "in-chip "multiphoton lithography, can also be utilized to fabricate complex nanoarchitectures into classical microfluidic platforms [112]. The 3D printing techniques for the chips' functional elements (such as valves, pumps and sensors) will not be further discussed in this review, and readers are referred to Weisgrab et al. [106].

Regarding fibre manufacture strategies, the microfluidic system-associated flow usually follows a **core-sheath flow geometry** [71,81,113–119]. This geometry is characterized, as the name suggests, by polymerizable/pre-polymer solution(s) as the core (inner) flow and non-polymerizable fluid as the sheath (outer), in which the sheath flow evenly surrounds the core flow in all directions [21]. Supported by the principles of microfluidic hydrodynamic shaping, two main sub-geometries can be differentiated: concentric/coaxial flow (**Fig. 2**) and cross-flow (**Fig. 3**) [72]. The concentric/coaxial strategy allows the direct formation of core-sheath flows and easy regulation of fibres' diameters by adjusting input flow rates [20,120]. In cross-flow geometry, hydrodynamic focusing determines the shaping of one flow by another, since, conversely to concentric geometry, the core and sheath flows are introduced in-plane with some angle of incidence between them [121]. With this setting, the fluids' viscosity ratio, length-to-diameter microchannel ratio and viscous dissipations are critical parameters [72]. T-junction microchannels are a typical example of this geometry [122,123].

Several pump-associated inlets can be employed to form both the core flow (inner channels) and the sheath flow (outer channels), resulting in a laminar flow regimen in such devices. After solidification, polymeric fibres are continuously generated in the microchannel and exit through an outlet channel. In 2004, Jeong et al. presented the first core-sheath microfluidic device which produced fibres without touching the PDMS microchannel's wall, as the result of this setup. This work also first reported the ability to produced hollow fibres, by adding a secondary inert fluid to the core flow to microfluidic device [20].

Considering a typical tubular coaxial microchannel, the radius of the core flow (R_c) can be mathematically determined based on flow rates and microchannel's cross-section area, as described below (**Eq. 3** and **Eq. 4**):

$$R_c = \left(\frac{S}{\pi}\frac{Q_c}{Q_s + Q_c}\right)^{\frac{1}{2}} \quad \textbf{(3)}$$

or

$$R_c = R\left[1 - \left[\frac{Q_s}{Q_s + Q_c}\right]^{\frac{1}{2}}\right]^{\frac{1}{2}} \quad \textbf{(4)}$$

Where R represents the channel's cross-section radius, S is the channel's cross-section area, Q_s and Q_c are the volume flow rates of sheath flow and core flow, respectively [11,27,72]. Thus, on a tubular microchannel and according to these equations, the fibre's diameter can be tuned by simply varying the input flows (sheath and core) and adjusting the ratio between them, without even altering the systems' setup. It thus becomes clear the relationship between flow rates and the fibre's diameter – greater the sheath flow, smaller the fibre's diameter; greater the core flow, greater the fibre's diameter (with other constant factors).

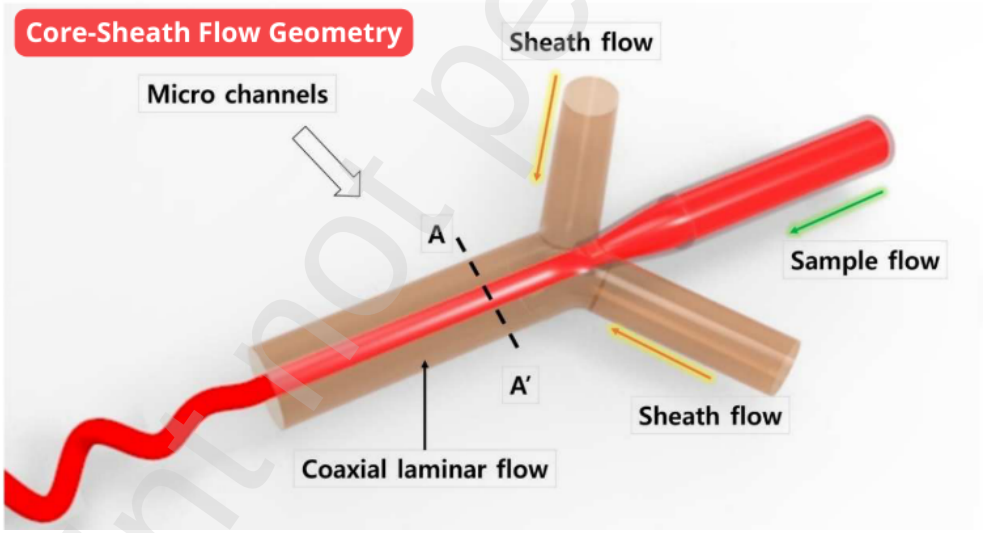


Fig. 2 – Core-sheath flow geometry in a microfluidic device. Reproduced with permission from Cheng et al. [38] Copyright Elsevier 2017.

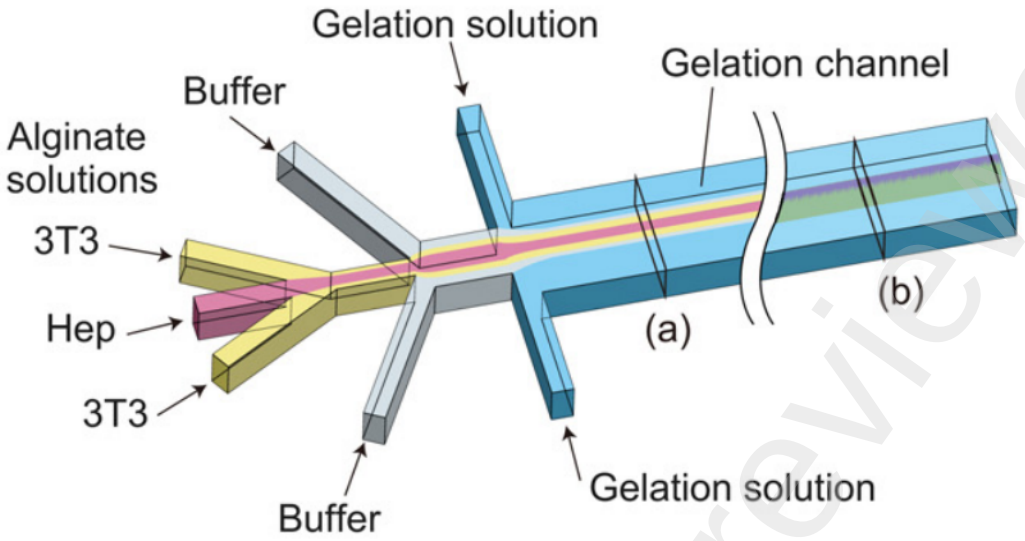


Fig. 3 – Cross-flow microfluidic device for the manufacture of sandwich-type alginate hydrogel microfibres which incorporate hepatocytes (Hep) and 3T3 cells. Reproduced with permission from Yamada et al. [121] Copyright Elsevier 2012.

Conversely, the effect of actual channel shape on the fibres' mechanical properties is not entirely clear. Nonetheless, Xu et al. recently designed a protocol which produced biocomposite fibres using different core channel shapes on a PDMS/glass chip (**Fig. 4**). They concluded that the channel's shape significatively influences flow fields (shear and elongational), hydrodynamic behaviours of molecular clusters, the morphology of fibres, and particularly their tensile performances [118].

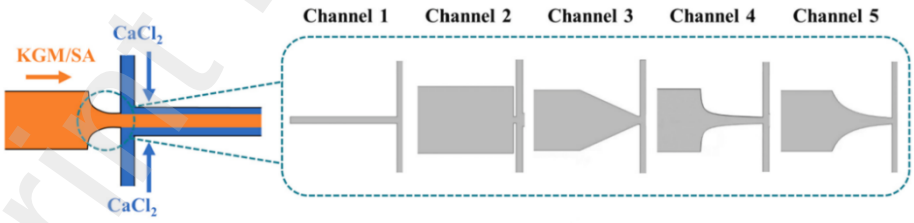


Fig. 4 - Structure and shapes of the confluence region of channels. Straight (Channel 1), sudden finish (Channel 2), linear contraction (Channel 3), constant acceleration (Channel 4), and increasing extension rate (Channel 5). Reproduced with permission from Xu et al. [118] Copyright Elsevier 2023.

Although core-sheath flow is the most generally employed type of geometry in microfluidic spinning technology, some researchers have also tested geometries without making use of a surrounding sheath flow. **No-sheath flow geometries** may increase production feasibility, by reducing flow inlets and simplifying geometries/requirements, but their microchannels tend to be easily clogged (due to absence of sheath flow [124]) and, consequently, the control of the reaction variables becomes more difficult [67]. Costa-Almeida et al. combined both microfluidic spinning technology and polyelectrolyte complexation, another common technique for fibre production, and produced multi-component hydrogel fibres with fibrillar-like structure. By injecting two oppositely charged polyelectrolyte solutions (methacrylated hyaluronic acid/chondroitin sulphate; and alginate) into a simple Y-shaped microchip, the authors were able to generate hydrogel fibres via electrostatic interactions between the solutions, without utilizing a sheath flow [125]. In 2020, Li et al produced silk fibres from silk nanofibres dispersed in formic acid, using bioinspired microfluidic chips. Mimicking a native silk gland, the PDMS microchannel geometry had a funnel-like feature, in which integrated shearing and elongational phenomena took place. The formed fibres presented aligned hierarchical structures, without employing sheath flow [67].

In order to further expand the devices' geometry and increase microfluidic-related versatility, some **complex geometries** have been tested, which diverge from the previously mentioned geometries. Three-dimensional hydrodynamic focusing has been used in this context to laterally focus the core fluid into a vertical stripe (with the same height as the channel). The width of such stripe and its cross-section are thus determined by the flow rate ratio between sheath and core flows, and by the angle of incidence between the inlet fluids [72,126,127]. A three-dimensional strategy, such as the aforementioned, can be remarkably favourable for complex microfluidic geometries. For instance, a series of recessed grooves can be patterned into the floor and/or ceiling of the microchannel, resulting in flow-focusing and flow-shaping properties. These grooves are set downstream of the initial focusing region and there generate fluid advection perpendicular to the channel's axis. This phenomenon creates vertical focusing (displacing the core stream vertically), while the number of inlet and channel grooves shape hydrodynamically the core flow into tuneable 3D fibrous designs [68,113,127,128]. It was also reported that different types of grooves are intimately linked with different fibre shapes, such as chevron, diagonal and herringbone [129].

Some researchers have also designed pulsatile microfluidic devices, which are able to precisely control flow segmentation accordingly to desired fibre lengths [130]. Aiming to optimize this strategy, Martino et al. reported the construction of alginate fibres with lengths between 200 and 1000 µm from an alginate solution and a Ca^{2+}-containing buffer solution on a simple microchannel. Although this geometry's usefulness is obviously limited, the highlighted advantage rests on the effortless

cutting/segmentation since it can be done with only a few millibars of pulsatile pressure (without interfering with the down-stream flow). The authors also employed such geometry to successfully incorporate these segmented fibres into microdroplets (down-stream) in the same microfluidic device [131].

On a different approach, some microfluidic researchers tested the combination of microfluidic spinning with solution blow spinning (similar to dry-spinning), where microfluidic devices fabricate liquid microjets based on a gas dynamic virtual nozzle (GDVN) (**Fig.5**) [132]. Solution blow spinning fundamentally makes use of the Bernoulli's Principle, in which changes in flow pressure are converted into kinetic energy. In this case, as the high-pressure gas stream exits the outer nozzle, the pressure quickly drops to atmospheric pressure, increasing the kinetic energy of the stream and resulting in increased sheath gas velocity. Consequently, a region of low pressure around the inner nozzle is produced, which is responsible for the acceleration of the polymer solution. This induces shearing at the gas/solution interface, deforming the accelerated core polymer solution exiting into a conical shape, which then originates fine streams of polymer solution after solvent evaporation [132–134]. Prominently, this method, combined with a microfluidic nozzle (GDVN-microfluidic device), enables the continuous production of micro/nanofibres, whose parameters are mathematically described and, therefore, can be precisely tuned accordingly to final fibre diameter and properties [135].

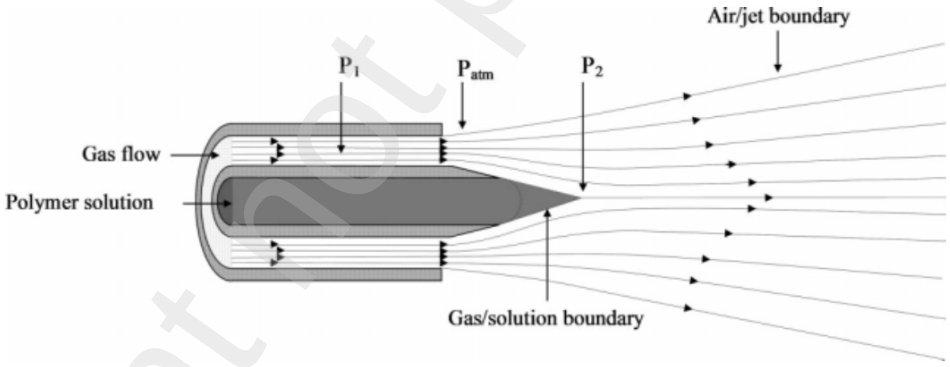


Fig. 5 – Solution blow spinning device nozzle. (P_1) – gas stream pressure; (P_2) – low pressure region; (P_{atm}) – atmospheric pressure. Reproduced with permission from Medeiros et al. [132] Copyright Wiley 2009.

Spindle-knotted microfibres are another evident example of complex microfluidic geometries. To manufacture these heterostructured fibres, a microfluidic system capable of integrative joint spinning, fluid coating, and knot emulsification processes, must be employed. Shang et al. developed a coaxial

capillary microfluidic device, in which spinning occurs when a core sodium alginate liquid flow is injected into a Ca^{2+}-containing middle (pre-gel) flow. This controllable sheath flow acted as a coating solution for the spun microfibres. The coating was then emulsified due to contact with an immiscible outer fluid and broke into spindle-shaped knots on the microfibres. Unlike conventional microfluidic systems, this geometry enables precise droplets formation/coating along the microfibres (knots) by controlling the flow rates and fluid viscosities [116]. According to Plateau–Rayleigh instability, the controlled viscous coatings break into droplets due to surface tension. Notably, the size and spacing of the spindle-knots could easily be controlled by adjusting the middle and outer flows [136]. Using a similar capillary-based system, He et al. constructed magnetic spindle-knotted composite microfibres, which were structurally similar to spider silk. The group used an oil phase of ferrofluid (magnetic features) in the central inlet, which was then sheared by an alginate solution jet flow, forming monodisperse magnetic oil drops. The alginate middle flow was then shaped and cross-linked by a $CaCl_2$ solution sheath. These structural features highlighted the fibres' potential as building blocks for complex 3D scaffolds for water collection, cell culture and overall tissue engineering [76].

As mentioned, by simply adjusting the microfluidic channel's geometry and inlet flow rates, the produced fibre's structure and size can be precisely controlled and optimized [39,137]. Thus, it becomes relatively straightforward to form fibres with diverse shapes, namely solid [138], porous [139], tubular/hollow [22]; hybrid/Janus [140], flat [120], grooved [79], and (nanoscaled) crystal-like [101,141]. Additionally, the fibre's cross-section and the secondary structure (such as, straight [142], waved [143], helical [137] and knotted [144]) can also be accurately designed on specific microchannel's shapes and flow ratios [11,103]. In a clear example regarding the potential of MST on fibre morphology design, Pham et al. prepared self-assembled alginate hollow microfibres. The formation of a hollow structure was achieved on a simple PDMS Y-shaped chip by using an alginate polymer solution as sheath flow, while using a $CaCl_2$ solution as the core flow and cross-linking agent. The authors concluded that the hollow fibre's outer diameter was independent of the flow rates, while the internal diameter and wall thickness were found to be clearly determined by both the core and sheath flow rates. Using a constant sheath flow, with increasing core flow rates, the internal diameter increased while the wall thickness decreased. Conversely, with a steady core flow, when increasing sheath flow rate, the internal diameter and wall thickness both decreased [105]. This relationship between fibre morphology and processing parameters undoubtedly reflects microfluidics' highly versatile and controllable/tuneable profile, and the ability to further expand the morphology of the fibres.

3.3. Solidification methods of microfluidic spinning of fibres

Within these microchannels, the fibre precursor solution requires to be cured into a solid material. An appropriate solidification method is therefore also crucial in obtaining the desired fibre morphology based on the raw material choice [1,101]. In conventional wet spinning, the fibre's solidification is based on a simple solvent exchange process, while in microfluidic spinning technology there are a range of currently employed curing methods, which are intimately connected to the diversity of the fibre materials. Currently, the most typically used solidification methods are (UV)-photopolymerization, ionic crosslinking, chemical crosslinking, and solvent exchange [11,38], as illustrated in **Fig. 6.** Considering **photopolymerization**, photopolymerizable monomers (such as PEGDA, 4-HBA, etc.) are normally used as the backbone material, while photo-initiators are added to induce the radiation-linked polymerization process and, consequently the fibres' fabrication. This cross-linking method is relatively simple, stable and controllable, and enables flexible fibre geometries (by regulating UV intensity and exposure time) [145]. However, applications are restricted due to the potentially harmful influence of UV radiation over biological materials (such as cells and non-biodegradable materials), thus tissue engineering functions can be particularly limited [11,20]. **Chemical crosslinking** is commonly used to produce biodegradable and biocompatible microfibres (for a few materials only), through the formation of covalent or noncovalent bonds between the polymer (core fluid) and cross-linker monomers (sheath fluid) [146]. **Ionic crosslinking** is the most widely utilized method, greatly due to the extensive use of alginate crosslinked fibres. Supported by the presence of divalent cations in a cross-linker solution (typically Ca^{2+}), ionic bonds are formed with the polymer's negatively charged groups. The resulting biodegradable fibres are particularly desirable for cell incorporation/culture, tissue engineering and overall biomedical applications, although they tend to display poor mechanical performances, as seen in non-composite fibres [102,114,118,147,148]. **Solvent exchange** techniques involve diffusion-based mass exchange between the polymer solution and a non-solvent (precipitating reagent). This differential solubility method generates polymerized fibres from a diversity of backbone materials, especially synthetic polymers, such as (PPDO-co-PCL-b-PEG-b-PPDO-co-PCL) amphiphilic triblock copolymers [139], PLGA [71], PMMA [113] and PCL [149]. However, frequently used solvents for this solidification method are generally toxic.

Although there are other relevant methods, such as nonsolvent-induced phase separation [116] and solvent vaporing or evaporation [45], the lack of design and material flexibility have limited wider usage [11].

Evidently, the selection of the optimal cross-linking method is intimately related to the polymers employed. For example, **ion-based cross-linking** is used to form fibres from alginate, chitosan,

vanadium pentoxide (V_2O_5), among others [38]. $CaCl_2$ solutions are frequently chosen to cross-link alginate [75,79,120,150] and V_2O_5 fibres [115], while tripolyphosphate (TPP) is used for chitosan cross-linking [114,147]. In PLGA microfibres, **solvent exchange** has been utilized to form fibres. Hwang et al. showed, by using a core PLGA solution (10% in DMSO) and a sheath glycerine/water solution (50% [v/v]), an exchange of DMSO and water occurred between core and sheath flow, thus solidifying the PLGA polymer [71,151]. As for gelatine-hydroxyphenyl propionic acid (Gel-HPA), **chemical cross-linking** has also been utilized. Hu et al. reported that an enzymatic reaction, which involved horseradish peroxidase enzyme (HRP) and hydrogen peroxide, triggered polymer solidification for Gel-HPA fibres (H_2O_2) [138,152].

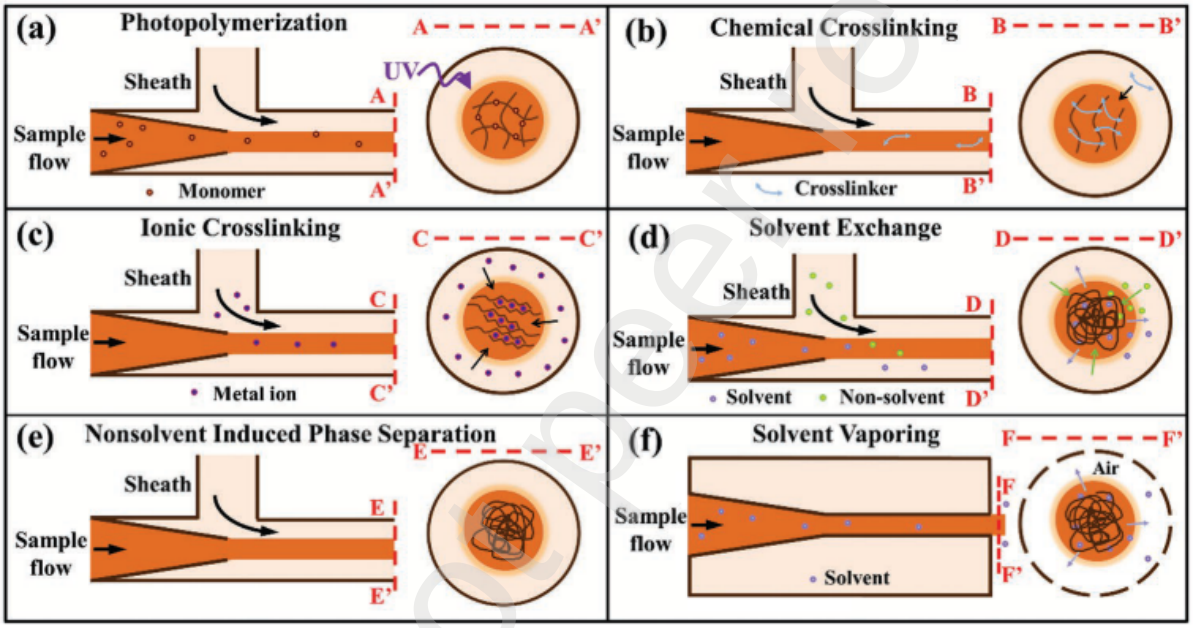


Fig. 6 - Schematic diagram of different solidification methods for fibre fabrication via MST. Currently the most relevant are a) photopolymerization; b) chemical crosslinking; c) ionic crosslinking; d) solvent exchange; e) nonsolvent-induced phase separation; f) solvent vaporing. Reproduced with permission form Du et al. [11] Copyright Wiley 2019.

4. Polymer materials for microfluidic-spun fibres

Natural polymers or biopolymers, as the name suggests, are obtained from biological sources. They can be produced directly by living organisms (via biosynthesis) or chemically synthesized from biological material [153]. They can be divided into three categories (based on the monomer's nature): (i) polysaccharides, (cellulose, chitin, alginate, etc.); (ii) polypeptides (collagen, silk fibroin, etc.), and (iii) polynucleotides (DNA and RNA) [154]. When compared to synthetic polymers, biopolymers stand

out due to favourable barrier performance, biodegradability, biocompatibility (usually reduced antigenicity), biomimicry (structural/compositional similarity to natural ECM), low weight, low cost, and renewability feature. Additionally, due to growing environmental awareness and demand for fossil fuel reduction, biopolymers have gained increased interest and are gradually replacing synthetic fibres, which lack renewability [153,155–157]. However, some natural fibres present inadequacies such as poor tensile strength and unpredictable performances [35,37,155,158]

On the other hand, synthetic polymers usually possess adequate mechanical properties, design flexibility, processing capability, reproducibility, durability and chemical stability [39,153]. Most synthetic materials have also low immunogenicity potential, though they lack bioactivity. Moreover, biopolymers hold improved potential for *in vivo* applications, due to their advantageous cell-interaction moieties [159].

Microfluidic spinning is much more suitable for natural polymers, compared to electrospinning due to the mild spinning conditions, absence of toxic organic solvents, normally aqueous environment, ability to handle single fibres and uniformity in fibre size/shape, which are inherent to MST and enable the use of sensitive (bio)materials, such as proteins and cells. Conversely, electrospinning, is likely to denature such biomaterials [38].

Concerning absorbable and nonabsorbable fibres, i.e. with high and low degradation rates in *vivo* respectively, recent studies have reported no significant difference between the two in terms of mechanical performance and/or bioactivity [50,160,161]. Nonetheless, in the case of fibres as sutures, absorbable fibres prevent the need for potential secondary surgery, leading to reduced patient-related anxiety/fear during the wound healing procedures [162]. Also, Yao et al. recently hinted that absorbable fibrous sutures possess added advantage in improving cosmetic appearance [163] , while other authors additionally reported reduced overall economic cost in total knee arthroplasty surgery with absorbable sutures, due to reduced incidence of fatty liquefaction, less frequent need for gauze change, and shorter postoperative length of stay [164].

4.1. Natural materials

4.1.1. Collagen

Collagen, catgut's main component, was one of first fibrous materials used for biomedical purposes, specifically as catgut sutures [35]. **Collagen** fibres, mainly composed of type I collagen, are the core component of connective tissue and skin in mammals. This fibrous protein is arranged in a rod-like helix structure and is still widely applied in biomedical sciences, due to excellent biological and physicochemical properties, unique biocompatibility and biodegradability profiles, and self-assembly behaviour [165]. However, pure collagen commonly exhibits several shortcomings, namely large

hydrophobicity, insufficient mechanical strength (for some applications), accelerated biodegradation and high bacterial deterioration rate *in vivo* [81]. Numerous authors have reported functional enhancements and "extraordinary mechanical properties" [166], particularly through cross-linking optimization and composite fibre assembly, using a diversity of microfluidic spinning systems and reagents [81,109,167–169]. Yue et al. reported the preparation of a novel type of collagen antibacterial composite fibre with remarkable enhancements on the fibre's structure, thermal stability, and mechanical properties. Using a multichannel microfluidic chip, a tannic acid-grafted collagen solution was used as the core flow, anhydrous ethanol as the sheath flow, and $AgNO_3$ solution as the spacer flow. Tannic acid (TA) not only strongly crosslinked collagen fibrils via hydrogen bonds, but also chelated with Ag^+, providing a functional antimicrobial feature to the collagen fibre [81].

An appropriate cross-linking treatment is undoubtably crucial for optimizing collagen fibres' value. In this regard, Zhang et al. observed that a second cross-linking treatment with glutaraldehyde further increased the breaking strength, Young's moduli and toughness of microfluidic-spun collagen fibres, with values comparable to those of regenerated silk fibres [170].

Noticeably, it was also recently disclosed the important role of glycosaminoglycans (GAG), ECM's main structural biomolecules alongside collagen, on the biophysical properties of collagen-based fibres/hydrogels, namely regulating the matrix microarchitecture of hydrogels during collagen fibre self-assembly. Thus, collagen-GAG composite hydrogels hold great potential in tissue engineering, due to their enhanced features and striking similarity to native ECM [171].

4.1.2. Gelatine

Gelatine consists of a partially hydrolysed and degraded collagen form which is obtained from various tissues of mammalians, and even fish [138,172]. Similar to conventional collagen, gelatine presents excellent biocompatibility, low immunogenicity, easy manipulation, and biodegradability, thus holding great value for biomedical applications [173]. However, it was gelatine methacryloyl (GelMA) form, also named photo-crosslinkable gelatine, which earned widespread interest of biomedical researchers. GelMA enabled more robust features and applications since conventional gelatine is quickly dissolved at body temperature, and has a cumbersome solidification method. Its viscosity is amenable for microfluidic technologies, enabling GelMA fabrication into diverse formats, namely micro/nanofibres and 3D tissue scaffolds with extensive applications in research of tissue engineering, drug delivery, organ-on-a-chip, and biosensors [174]. Also, using microfluidic spinning, GelMA-based composites are easily obtained and display enhanced polymer properties, such as higher mechanical

moduli, better stretching performance and lower swelling [175], and hence have been expanded to further biomedical applications [68,79,172,176].

Gelatin–hydroxyphenylpropionic acid (Gel-HPA) is yet another relevant gelatine-derived polymer whose hydrogels favourably present high porosity and biodegradability. Hu et al fabricated hydrogel fibres with diverse shapes by enzymatically cross-linking solutions containing cell-mixed, and fast-gelling Gel–HPA conjugates, in a microfluidic device. Physiochemical properties were carefully optimized based on the desired application, since the adjustment of mechanical strength interfered with cell incorporation and alignment, thus jeopardizing 3D cell culture/transplantation applicability [138,152].

4.1.3. Chitin/chitosan

Chitin is an eco-friendly and biologically inert natural polymer which can be obtained from crustacean or fungal cells' walls. Chitin is characterized by having cheap raw material sources, alkaline feature and high charge density (enabling metal chelation) [177]. Chitosan represents a derivate material, originated from structurally refined chitin (50%+ deacetylation) and exhibits superior solubility and broader antimicrobial properties [178]. Chitosan (and chitin) showed enhancement in fibroblast migration and proliferation, consequently promoting vascularization and granulation, while also presenting anti-inflammatory features [179]. These qualities are noticeably convenient in wound healing processes. Chitosan, however, seems to have faster biodegradation profile [180] and relatively poorer mechanical properties. Additionally, chitin fibres are generally produced via wet-jet and dry-jet spinning [177], while functional and well-designed chitosan fibres have been recently obtained via microfluidic spinning [147,148], which is a more advantageous manufacture approach, as mentioned.

4.1.4. Alginate

Currently, **alginate** is one of the most commonly employed biomaterials in biomedical science and engineering. This linear polysaccharide is widely used in spinning techniques due to its favourable properties, including biocompatibility, ease of gelation (hydrogel formation) and stable mechanical features, although insufficient for some applications [24,181,182]. Particularly desirable in wound healing, drug delivery, and tissue engineering applications, these (sodium/calcium) alginate hydrogels retain strong structural similarity to extracellular matrices (ECM) in tissues and, furthermore, their structure can be easily tuned according to desired application and/or composition [58,65]. Alginate actually represents a whole family of linear copolymers containing blocks of β-D-mannuronate (M) and α-L-guluronate (G) residues. Alginate hydrogels' mechanical properties are closely determined by with the number of (G)-blocks and overall molecular weight, which can be tuned. However, by increasing the number of (G)-blocks, the viscosity also increases greatly, which might become

incompatible with microchannel processing. Thus, a favourable tunability approach consists in combining high and low molecular weight alginate polymers [183]. Currently, alginate is extensively exploited to fabricate cell-laden fibres, since this protein polymer enables viable cell incorporation, holds a well-established cross-linking process ($CaCl_2$ as crosslinker) under mild processing conditions, and has a simple microfluidic production process. Alginate allows a variety of alginate (composite) fibres and a consequential expansion in terms of their biomedical applications, especially in tissue engineering applications [40,68,118,119,150,181,184,185].

4.1.5. Silk

The term silk refers to continuous protein-based fibre-forming materials [186] and represents the most relevant microfluidic spinning material, since it was silk spinning by living organisms that inspired the development of microfluidic spinning technologies. Konwarh et al even labelled biospinning as “nature's signature microfluidic-manoeuvre" [187]. In fact, through biomimicking the silk glands and spinning duct of silkworms (*Bombyx mori*), microfluidic chips were developed and enabled the controllable nanoscaled synthesis of this biopolymer. Silkworm silk fibres are in fact composites made of two different proteins: fibroin (core structure) and sericin (gummy sheath). Silk’s applicability derives of fibroin polymers, after degumming [141]. Silk from orb-web-weaving spiders consists of spindle-knot spidroin core threads coated with glycoproteins [28,116]. Native silk’s is indeed a fascinating material, since it is as strong or stronger than steel, yet six times lighter and flexible [188,189]. Nonetheless, farming spiders for silk is practically impossible and producing recombinant spider silk has still significant high costs [170]. Thus, regenerated silk fibroin is more commonly used in most applications [134]. Silk-based materials are known to be extremely resistant to *in vivo* degradation (up to 2 years) [190], and therefore silk is classified as a non-degradable/non-absorbable biopolymer-based material. High mechanical strength, biocompatibility, low bacterial adhesion and immunogenicity, self-assembly capability, and versatile processability are defining advantages of regenerated silk fibroin fibres [186,191–193].

Using microfluidic approaches, silk fibroin has been successfully spun into composite fibres [116] and crystal-like ordered fibres [141], with remarkably tuneable degradation rates and surface functionalization. However, artificially spun silk fibres seem to not yet approach native silkworm silk’s mechanical strength, so new approaches have been tested with encouraging results [194].

Additionally, even though silk, as a material, is not directly involved in most microfluidic-fabricated fibres, these are commonly constructed using the mentioned silk spinning mechanism of the silkworm [136,141], which emphasizes the role of silk as a crucial piece in microfluidics development.

4.1.6. Cellulose

Cellulose is a natural linear polymer of β-D-glucose units (linked via β-ether bonds). As an example of an eco-friendly biopolymer, cellulose can be easily obtained from plants since cellulose nanofibrils are the main structural components of plant walls. This polymer is the most abundant on Earth as it also is produced by microorganisms (named bacterial cellulose), such as algae, fungi, and some bacteria. Cellulose derivatives are often preferred over pure cellulose, due to better water solubility profiles, low cost, favourable biocompatibility and biodegradability. Amongst these, cellulose acetate, methylcellulose, carboxymethylcellulose, and hydroxypropyl cellulose are the most advantageous for biomedical applications [195,196]. Cellulose-based (nano)materials are remarkably useful for the fabrication of functional nanoarchitectures, due to their self-assembly feature. The main concern when employing cellulose materials rest on inherent biological variability, as cellulose of different origins may present significatively distinct features. For example, sisal cellulose fibres were found to have inherently weak mechanical strength but considerable antifouling properties, which are highly compatible with suture application [197]. Cellulose fibres can be fabricated using a plethora of methods, although the microfluidic approach enables the controllable production of composite fibres. The hybridization of cellulose with other polymers/components is an answer to overcome intrinsic shortcomings via tailoring the physicochemical and functional properties [80,198,199]. Concretely, Ding et al produced fibre-type composite dressings containing cellulose, which presented enhanced mechanical features, excellent breathability, antibacterial and haemostatic qualities. Based on microfluidic spinning technology, an aqueous mixture of polyvinyl alcohol, microcrystalline cellulose, *Euphorbia humifusa* wild extract, and sodium alginate was used as the core flow on a simple coaxial capillary system. The sheath flow consisted of $CaCl_2$ (cross-linking agent) solution. The microspun fibres were then arranged into dressings and reported enormous potential for wound healing applications [119].

4.2. Synthetic materials

Although, as mentioned, synthetic polymers tend to display better mechanical properties and design flexibility, the growing environmental concerns and the lack of critical bioactivity resulted in less biomedical investigation of these polymers, compared to natural fibres [39,159]. This statement is supported by the comparatively smaller presence of synthetic polymers in literature. Nonetheless, some synthetic polymers have also been used in microfluidic fabrication of (composite) polymer fibres, namely the following.

Poly-lactic-co-glycolic acid (PLGA) polymers are synthetized through a co-polymerization process involving cyclodimers of glycolic acid (GA) and lactic acid (LA) in a specific proportion [25]. Despite being a synthetic polymer, PLGA has a very suitable biocompatibility and biodegradability profile,

being classed as an absorbable polymer [200,201]. Moreover, PLGA presents an interesting thermoplastic and rheological profile, since it holds great mechanical strength and maintains a complex structure when thermally stretched [202]. Remarkably, its mechanical and (bio)degradation properties can be tuned by regulating GA/LA ratio. Some challenges restrict PLGA-based fibres applications, such as the lack of hydrophilicity [203], although these can be potentially overcome with chemical or bioconjugation with polymers/molecules. This strategy has rendered PLGA with functional features, which led Martins et al. to label this polymer as the "Holy Grail among synthetic polymers" in biomedical sciences [25].

Additionally, poly(ethylene glycol) diacrylate (PEGDA) [22], PMMA [113] and polycaprolactone (PCL) , polyurethane (PU) and its photopolymerizable derivatives [140], are some of other synthetic polymers which have been employed in microfluidic spinning technology. PEGDA is a particularly interesting photo-crosslinking hydrogel since it exhibits slow degradation rate *in vivo*, thus holding value as biocarrier for long-term drug release [204]. We highlight the role of synthetic polymers in composite fibres for biomedical purposes, rather than in monopolymer fibres. On this matter, Chen et al reported a three-fold increase in tensile strength when thermoplastic polyurethane nanofibres were enriched with carbon dots, via electro-microfluidic spinning [205].

5. Composite fibres for biomedical purposes

As previously described, different fibre-constituting polymers exhibit different physicochemical properties according to the base polymer, which translates into distinct advantages and limitations. For instance, natural polymer fibres usually display favourable cell affinity and biocompatibility but tend to lack adequate mechanical properties (shear strength, e.g.). Conversely, synthetic polymers, normally display the opposite traits. The hybridization of polymers stands, therefore, as an answer to overcome individual limitations of each base polymer and reinforce specific favourable properties [199].

This tailored fusion is the basis of composite or hybrid materials. Although the denomination "composite" still lacks some harmonisation, here we will refer to composites as materials which are composed of two (or more) physicochemically distinct components/materials. Hybrid heterogeneous composite materials present differentiated properties compared the individual components. The newly formed material can exhibit, for example, greater mechanical performance/strength, loading capacity (porosity/permeability), versatility in surface functionalization, biocompatibility, biodegradability, and/or cell adhesion and growth [199,206]. Currently, the synthesis of composite materials can involve a wide range of materials, namely metals, non-metal inorganics, polymers and small organic molecules [61]. Nonetheless, polymers clearly hold more value as composite materials

in the biomedical field, as previously justified, and thus polymer composites will be specifically addressed in following sections.

Polymer-based composites are assembled from a matrix (base) polymer into which a reinforcing polymer or molecule (filler) is embedded. The newly originated composite's properties arise from a synergistic effect, compensating gaps and exploiting advantages of the primary materials. Toward properly and rationally selecting the components, their compatibility and combined properties' adequacy must first be confirmed [155]. Natural fibre-reinforced polymer composites have been gaining popularity due to their excellent mechanical properties and considerable manufacturing advantages, as well as the fact that they provide a solution to environmental contamination, since natural fibres are an ideal reinforcing material for polymer composites. Polymer blending has also attracted much attention as it is a simple and cost-effective method for developing composite polymeric materials, and therefore expand the versatility for their commercial applications. However, it is necessary to distinguish the concept of "blend" and "composite". Blends consist of multiple polymers that are combined and form a single-phase system (homogeneous material), while composite represents a category of substances where two or more components are mixed collectively to produce multiphase systems. Hence, composites can be also interpreted as immiscible blends of two or more components which hybridize individual component's properties [207–209]. Accordingly, we will also consider, for example, cell-laden or nanoparticle-loaded fibres to be composites, in this review.

Owing to nanotechnology's introduction to composites, nanocomposites or nanohybrids have gained plenty of attention in recent years. Higher surface area/volume ratios and easily tuneable properties are the core benefits of this downscaling. The morphology and features of each component becomes increasingly important at the nanoscale, thus fabrication of nanocomposites should be carefully designed according to the desired applications. Noticeably, the use of nanofibrous polymer composites (NFPCs), on which at least one component is at nanoscale, holds great promise in biomedical applications, owing to enhanced mechanical/functional features [199].

5.1. Microfluidic manufacture of composite fibres

Naturally, only with feasible and cost-effective production methods can a technology really fulfil its promise. Microfluidic-assisted composite polymer fibres have been recently fabricated and generally shown satisfying results. This approach is remarkably suitable for biocomposites [210], as it avoids harsh conditions experienced, for instance, in electrospinning (high voltage/organic solvents [211]). Microfluidics' mild conditions allows unproblematic biomaterial processing, even in an eco-friendly

manner [157]. Moreover, microfluidic synthesis shows also advantageous alignment capabilities, resulting in further enhancement in functional mechanical properties, such as reported for aligned Au- and CNTs-composite collagen fibres. Specifically, Spiaggia et. al used a simple single-phase microfluidic device (**Fig. 7**) to align and orient composite collagen fibres, employing a PDMS chip under generally constant conditions. A NaOH aqueous solution was used as the sheath flow and cross-linking agent. Gold nanoparticles and carbon nanotubes (CNTs) were dispersed in a collagen solution, as the core flow [169].

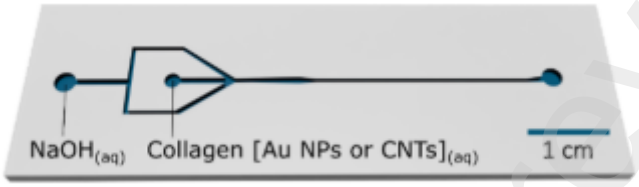


Fig. 7 - Schematic representation of the microfluidic device used to align and orient collagen fibres indicating the solutions injected in each of the inlets. Reproduced with permission from Spiaggia et al. [169] Copyright American Chemical Society 2021.

Apart from most commonly employed system types (single-phase co-flow), a multiphase flow in coaxial glass capillary device successfully fabricated complex bubble-filled silica composite microfibers. The device incorporated three inlets: a single central core gas (G) inlet and two liquid inlets for water phase (W) and oil phase (O), using tapered cylindric and squared capillaries. As the gas and two liquid phases flowed into the device, microfluidic-associated hydrodynamic focusing took place, resulting in continuous bubble formation in the water phase (containing PEGDA polymer and silica nanoparticles). Simultaneously, the outer oil phase induces jetting of the bubble-containing water phase. The UV photopolymerization then consolidates this structurally complex polymer–nanoparticle composite. Additionally, the size and morphology of the composite fibres could be tuned by simply changing the flow rates and the rotation speed of the collection spindle. The highly flexible fibres could also be thermally stiffened [77]. The overall device scheme and fibre structure are illustrated in **Fig. 8.**

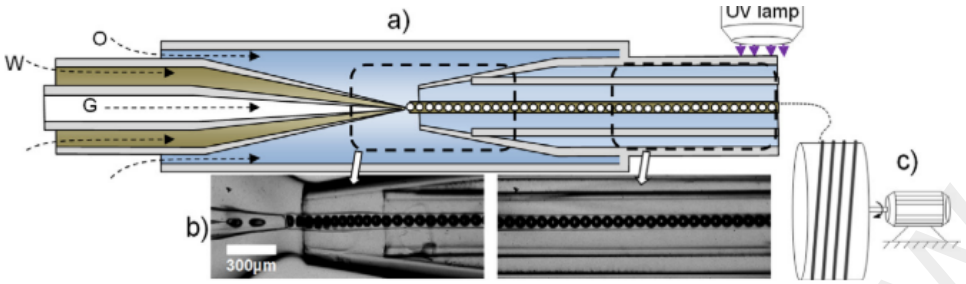


Fig. 8 - a) Schematic illustration of the glass capillary device and the generation of bubble-filled fibres. (b) Optical microscopy images showing bubble-filled fibre generation. (c) Fibre collection system with tuneable rotation speed. Reproduced with permission from Hou et al. [77] Copyright Elsevier 2016.

As previously introduced, Yue et al. recently prepared a novel type of collagen composite fibre via microfluidic spinning. The microfluidic wet-spinning system consisted of syringes pumps, a microfluidic chip, and a coagulation device. Illustrated by **Fig. 9**, five inlets microchannels and a straight outlet microchannel, all equal in diameter (200 µm), comprised the chip. Lyophilized collagen (polymer) was added to an acidic TA solution (cross-linking agent), forming the core flow. A $AgNO_3$ solution formed the spacer flow, while the sheath flow was anhydrous ethanol. This microfluidic geometry formed a solidified composite (TA-Ag) collagen fibre, which was jetted into acetone/ammonium hydroxide coagulation bath. The easily constructed fibres were then evaluated in terms of morphology, mechanical properties, structure, thermal stability, antimicrobial activity. Overall, this successful microfluidic approach enabled the straightforward manufacture of a functional composite fibre, which showed remarkable synergistic properties in terms of structure, thermal stability, mechanical properties and remarkable antibacterial features. These encouraging conclusions strengthen both the value and potential of microfluidic-spun composite fibres over conventional fibres. [81]

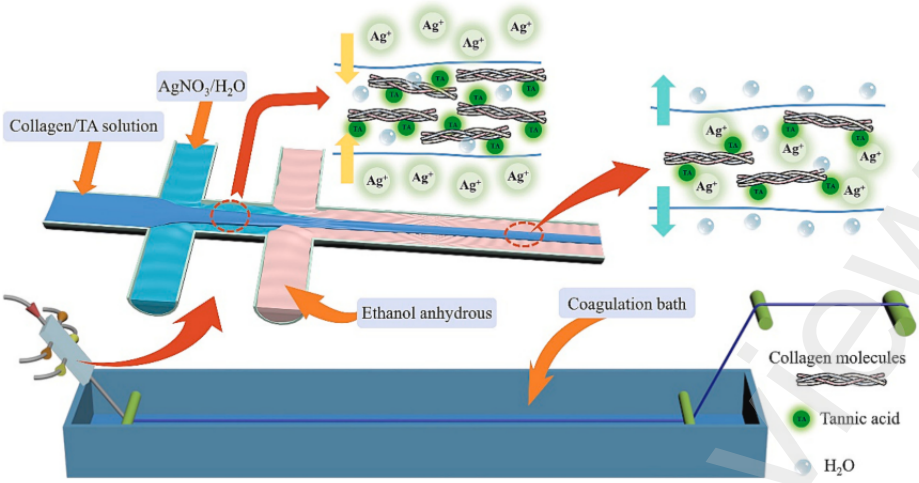


Fig. 9 - Schematic illustration of microfluidic spinning manufacture of the collagen composite fibres. Reproduced with permission from Yue et al. [81] Copyright Elsevier 2024.

The ability to construct complex (3D) fibre morphologies associated to MST is also favourably applicable to form enhanced composite fibres [136]. Esteras-Saz et al. prepared via microfluidics composite polysulfone/polyamide (PSF/PA) hollow fibres (arranged in membrane modules). Polysulfone hollow fibres, pre-configured in membrane modules inside a nylon tube, underwent a two-step interfacial polyamide polymerization after reagents' sequential injection, resulting in thin (PSF/PA) composite fibre membranes with accurate control of synthesis parameters. The incorporation of metal organic frameworks (MOFs) was also easily achieved through two distinct strategies (prior and posterior to PA polymerization, respectively), both forming polyamide/MOF bilayered nanocomposite membranes [5]. Wu et al. tested the versatility of microfluidics for complex composites even further. By combining a unique composite bioink (sodium alginate, gelatine methacrylate, and glycidyl-methacrylate silk fibroin) with optimized viscosity, microfluidic printing of vascular scaffolds, and latter microfluidic cell seeding/culturing, the authors constructed tuneable hollow microfibres and applied them in vascular tissue engineering as artificial blood vessels. They used a coaxial device (with a 3D printed holder), while the composite bioink solution constituted the sheath flow, and a Ca^{2+} solution served as the core flow. At the laminar flow interface, the bioink's sodium alginate was cross-linked with an immediate gelation transition (Ca^{2+} ionic crosslinking). A second crosslinking treatment was employed for the remaining polymers via UV light exposure. The resulting hollow composite fibre presented a favourable environment for cell adhesion and proliferation. So, an endothelial cell culture was introduced to the fibre's inner surface using a

perfusion device, which enabled retaining high cell viability and thus, enabling the fabrication of vascular-like tissue structures [212].

The use of computerized systems, increasingly present in current times, stand as another promising tool for composite fibres. As mentioned, microfluidics is a highly programmable (and automatic) approach, which may enable the construction of extremely complex fibres in a precise manner. By digitally controlling inlet flow injections on a microfluidic chip, Kang et al. fabricated microfibres with spatially diverse chemical compositions. By controlling chip's valve operation, the different materials were coded either via serial, parallel or mixed coding [213].

5.2. Biomedical applications of composite fibres

The biomedical applicability of these multiphase fibres is intimately linked with the concept of functional fibres, as these materials offer features beyond structural characteristics, namely tissue growth promotion, antiseptic/antimicrobial properties, drug coating/blending and stimuli responsiveness [60,79,156]. The functionalization of well-defined composite fibres can be attributed either to a specific fibre shape (hollow [214] and helical [215], for example), encapsulating functional materials (namely cells [216], proteins [139], drugs [217], silver nanoparticles [181], magnetic nanoparticles [218]), or fibre-spinning chemistry [219] (*in situ* ultrasmall-scale reactions).

Although microfluidic-spun composite fibres display obvious potential, this platform is only in its infancy in terms of biomedical applications [12,38,153]. Research articles regarding this subject have increased recently, but they still come short when compared to other technologies for fibre manufacture, namely electrospinning [220–223]. The (poor) commercial availability of spinning devices (microfluidic chips) was reportedly the main obstacle for this platform's development, however, today this issue has been partly surmounted based on recent estimates for compound annual growth rate of microfluidic chips market [224].

In this section, we aim to describe the current and most relevant biomedical applications for microfluidic-based composite polymer fibres in no particular order.

5.2.1. Wound healing

Microfluidic-spun fibres are exceptionally well suited for the fabrication of complex fibres considering the fact that they can yield intrinsically higher porosity/tuneable pore sizes and encouraging encapsulation of cells and cellular components within its matrix [146,217,225,226]. The resulting optimization of their mechanical and functional properties, with a single microfluidic device, is therefore highly desirable in the context of **wound healing** processes. The possibility to easily

incorporate antibiotics, growth factors, antiseptics, oncology drugs, and even DNA/RNA onto the fibre's porous structure, make these complex structures desirable for accelerated/optimized healing process. Ahn et al. reported the microfluidic production of ampicillin-loaded alginate microfibres and observed wound healing in rat's skin wounds. These antibiotic-loaded functional fibres were fabricated in PDMS microfluidic chips displaying a cylindrical and coaxial flow within the channels. An alginate/ampicillin aqueous solution was used as the core flow, while the sheath solution contained 3% (w/w) $CaCl_2$ in low-polarity isopropyl alcohol (IPA) or deionized water (DW). Also, coagulation baths were used to enhance the fibres' crosslinking, which employed 10% (w/w) $CaCl_2$ (IPA/DW) solutions, respectively. In conclusion, IPA sheath-based fibres showed condensed incorporation of ampicillin molecules and, consequently, a higher advantageous delay in degradation and release profiles (*in vitro* and *in vivo*) [217]. This simple and successful microfluidic spinning method paves the road for clinically applicable products emerging in the near future, while also extending its applications to other biomedical fields such as drug delivery.

The arrangement of composite fibres into scaffolds may be employed in wound dressings, where these fibres hold exceptional potential for wound healing. The structural similarity to ECMs, high surface-to-volume ratio and controllable porosity, facilitate cell adhesion and proliferation in wounded tissues and allow substance exchange (oxygen, water, nutrients and waste). Yu et al. used a double coaxial microfluidic device to develop copper- and zinc-MOF laden alginate hybrid fibres. This capillary device used hierarchically nested inner MOF phases of nicotinic acid (vitamin) which surrounded two immiscible precursor copper acetate and zinc acetate solutions as 3D coaxial core flows. Alginate shells encapsulated these MOF cores after $CaCl_2$ sheath flow triggered ionic cross-linking. Within the MOF cores, the copper added the anti-infection property, whereas zinc added oxidation resistance. When tested in murine models, both substances provided a better environment for wound healing. It was also reported that the physicochemical properties and MOF release kinetics could be further tuned by adjusting flow rates [227].

Mesoporous silica nanofibres (MSNFs) with controllable porosity are also promising microfluidic-based fibres, since they possess a versatile loading capacity which can optimize the fibres' functionalization and applications. To test this premise, Hao et al. designed a miniaturized spiral-shaped microfluidic device (two pump-associated inlets and one outlet), in which the material's great loading capacity enabled several substances to be successfully loaded into the fibres, such as antimicrobial agents (silver nanoparticles), chemotherapy drugs (doxorubicin) and growth factors. In this study it was also stated that MST enabled precise control over fibre morphology and size by simply adjusting the flow rates and the concentrations of the reagents [60].

5.2.2. Tissue engineering

The ease of modulation at nano/microscale and the use of mild ambient conditions are key advantages of the microfluidic approaches, which plainly enable biomimicry of different tissues and thus wide tissue engineering applications [101,228]. By precisely providing spatiotemporal control of the fibre's composition, size and morphology, microfluidic-spun composite fibres can be bundled, weaved or knotted into higher-ordered/hierarchical networks. These fibrous scaffolds can viably incorporate cells and even recreate artificial tissues, namely blood vessels [212], neural [229] and muscle fibres [230].

5.2.3. Cell incorporation

Undoubtedly, one of the major benefits of MST over other production methods is the ability to conveniently construct fibre-shaped cellular assemblies, under mild fabrication conditions and with high flexibility in morphology/size [230]. Therefore, cell immobilization, patterned co-culture, cellular immunoprotection *in vivo* [168] and biomimetic microchannels formations (hollow fibres) can be achieved and greatly contribute to the *in vitro* creation of fibrous organoids, with marked applications in tissue engineering [12,121,231–235]. Wei et al. photolithographically fabricated a PDMS microfluidic device for the continuous production of cell-laden hollow multilayered hydrogel microfibers, via syringe pumps. Human umbilical cord vein endothelial cells and (osteoblast-like) MG63 cells were added to an alginate solution. In order to form hollow composite alginate fibres, a non-crosslinkable hyaluronic acid solution was used as central flow and deionized water as the sheath flow, as illustrated in **Fig. 10.** After ionic- and photo-crosslinking, the final fibrous composite showed favourable cytocompatibility and regeneration features, while the microfluidic parameters displayed great tunability relative to the fibres' properties. The grafting of RGD (Arg-Gly-Asp) peptides improved cell spreading and proliferation, whereas mechanical strength was decreased. Nonetheless, the composite still displayed advantageous features with regards with tissue engineering applications [236].

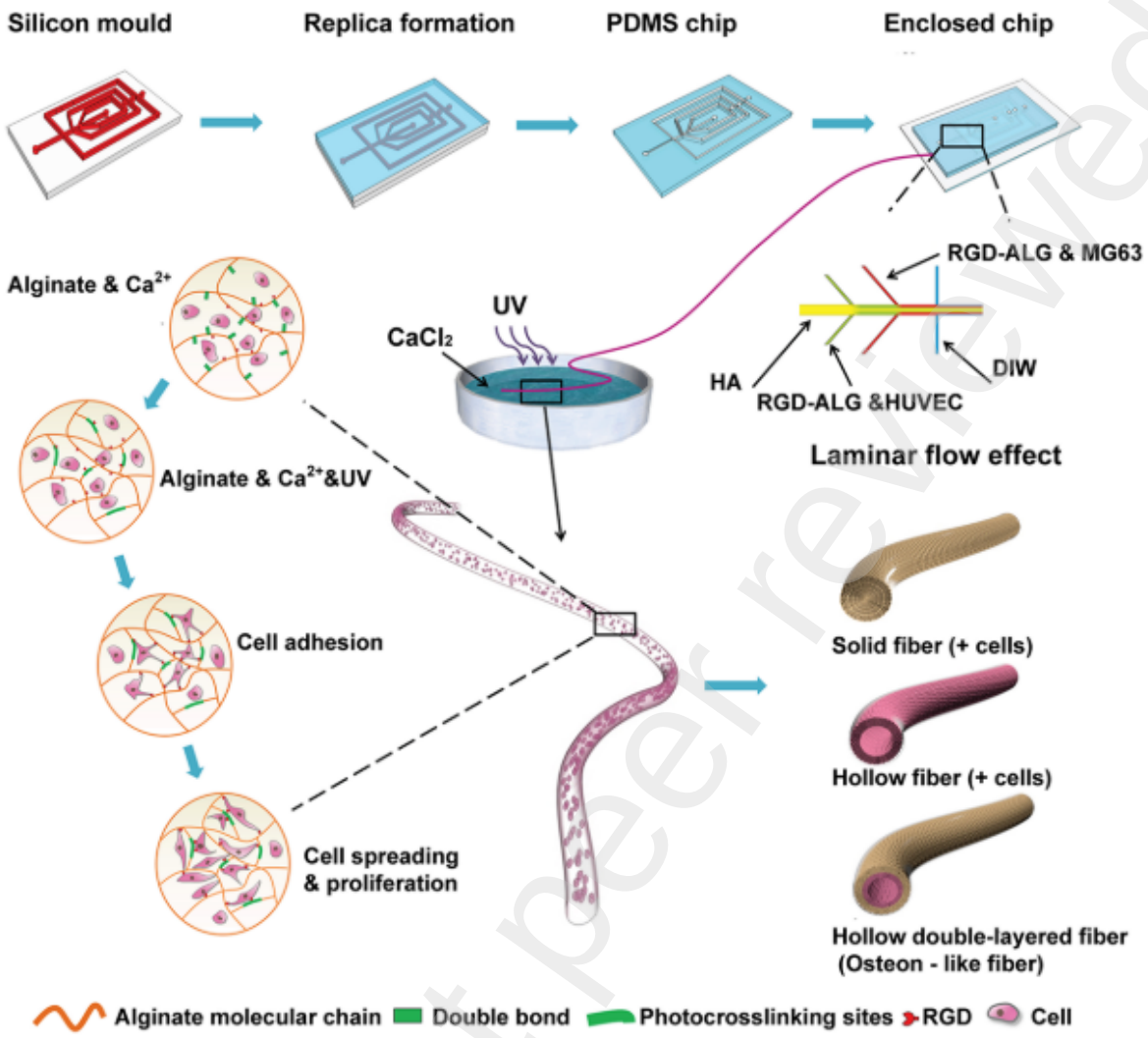


Fig. 10 - Schematic drawing of the fabrication of a microfluidic chip and continuous extrusion of cell-laden composite alginate fibres. Reproduced with permission from Wei et al. [236] Copyright American Chemical Society 2007. Publication licensed under CC-BY.

By safely encapsulating cells or cellular components within composite fibres, microfluidic devices offer immunoprotection against immune responses when applied *in vivo*. Jun et al. designed cylindrical PDMS chips following a single-phase coaxial flow design, as illustrated in **Figure 11**, to fabricate collagen/alginate composite (CAC) fibres with encapsulated pancreatic islets. The core flow consisted of a (1:2) collagen/alginate mix solution with suspended islets. The sheath flow was calcium chloride ($CaCL_2$) and was employed as the ionic cross-linking agent, with both flows controlled with syringe pumps. The extruded composite fibres presented uniform distribution of diameter and non-protruding islet encapsulation. Tests on streptozotocin-induced diabetic mice reported that normoglycemia was achieved after intraperitoneal implantation, which additionally confirmed

successful cell viability. This was attributed to the immunoprotection of transplanted islets from the host's immune reaction [168]. As such, composite fibres demonstrated their usefulness in functional cell transplantation, namely in encapsulation of pancreatic islets for type-1 diabetes mellitus treatment.

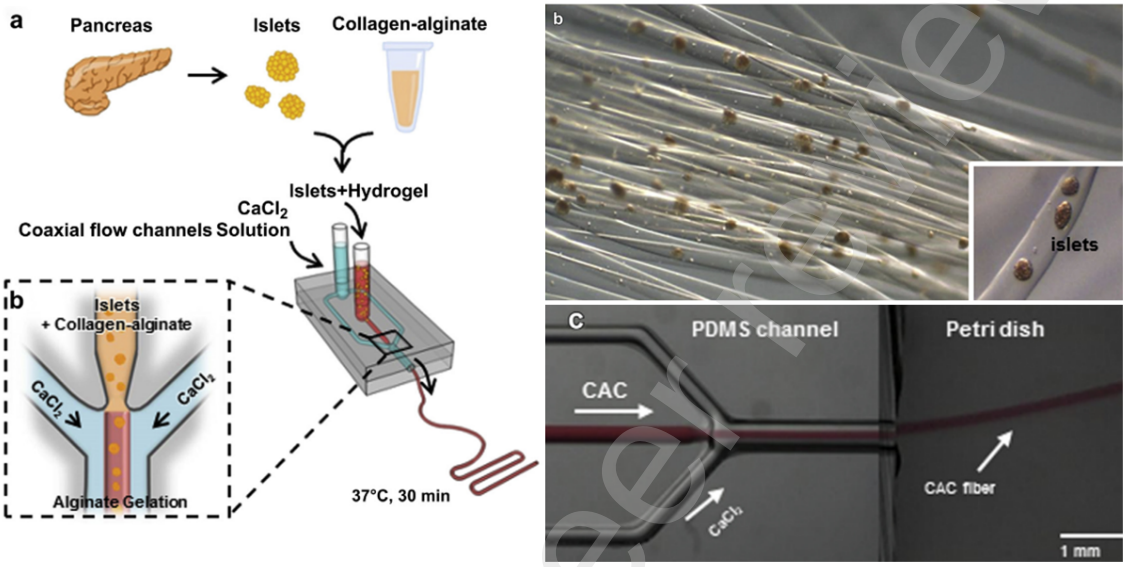


Fig. 11 - Schematic illustration of CAC fibre encapsulation. a) A collagen-alginate composite solution containing islets was used as a sample fluid, and a calcium chloride solution was introduced into the sheath fluid. b) The two solutions were mixed at the cylindrical outlet channel, inducing Ca^{2+}-dependent crosslinking of coaxially focused alginate to form the CAC fibre. c) Optical image of a CAC fibre containing islets. Adapted with permission from Jun et al. [168] Copyright Elsevier 2013.

Similarly, Lee and colleagues had previously produced alginate/chitosan composite fibres via a coaxial microfluidic device and, even employing a simpler design/geometry, HepG2 cells were also successfully incorporated into the fibre [65]. Several other articles also reported easily achieved cell incorporation into composite fibres in which diverse fibre morphologies were fabricated with diverse microfluidic systems, while exhibiting extended cell viability periods [96].

Besides enabling cell incorporation, the microfluidic approach additionally allows for exceptional cell alignment features. Just like electrospinning, MST is also able to induce secretion and deposition of anisotropic ECMs. However, electrospun fibres usually present poor alignment degree. Haynl et al. developed a simple core-sheath PDMS microfluidic device for collagen-based microfibres to test fibre alignment effects. Using a rotating spool to equalize flow and collection rates, highly ordered fibres

were continuously spun. Such optimization enabled greater cell alignment and axon growth using the NG108-15 neuronal cell line. Therefore, microfluidic-associated fibre alignment appears as yet another advantageous feature for tissue engineering and, particularly, for peripheral nerve repair [166]. Kang et al. also tested this functionality by employing a similar PDMS chip but with grooved channels, which generated cylindrical fibres with longitudinal microgrooves. This fibre morphology was found to be particularly useful in aligning cells along the direction of the grooves [213]. Aiming a larger quantity of incorporated cells, the authors spun thin flat grooved microfibres (microribbons) and concluded that guided cell culturing, allied to MST, could be directly applied in nerve regeneration procedures [120]. These fibres enable cell protection against mechanical stress and host's immune responses, while also facilitating bidirectional transport of nutrients, oxygen, and metabolic waste [101]. Overall, the microfluidic spinning of composite fibres is a highly promising platform for the creation of functional scaffold building blocks and patterned fibres for tissue engineering applications, such as large complex tissue repair of defects, regeneration of blood vessels, tendons, ligaments and skeletal muscles.

Another example in which microfluidic technology has gained traction is in the development of 3D cell-encapsulated fibre shapes for regeneration/support of damaged organs [21,101,237]. It is worthwhile mentioning that this platform could improve substantially if polymers other than alginate were used more often. Alginate is, undoubtably, the most employed polymer for cell-laden composite fibres, but it usually lacks mechanical strength [27,101], which therefore restricts its applicability as a single polymer in composite fibres, while other materials, such as silk [69,191] or PLGA [25,71], have shown a more advantageous profile for this particular end.

5.2.4. Fibres in (controlled) drug delivery

Drug delivery is also target of continuous biomedical investigation, noticeably in wound healing and local chemotherapy [38,217,238]. Although electrospinning has a more extensive track record in this field, microfluidic spinning-centred interest has also emerged, markedly for on-fibre delivery of biosensitive molecules or drugs. Commonly as hydrogels, these microfluidic-spun fibres can have excessively large pores and fast fibre degradation profiles, thus limiting drug delivery applications. However, avoiding this hydrogel form can circumvent this limitation. As shown by Ahn et al., an IPA-based solution as sheath flow, as an alternative to an aqueous one, enables the formation of a highly ordered crystal-like alginate fibre loaded with ampicillin, with a favourable release profile for drug delivery purposes [217]. More recently, Li et al. proposed a microfluidic 3D-printed fish-derived GelMA composite scaffold loaded with berberine, a phytocompound with anti-cancer properties. A single-phase, single-inlet (no-core-sheath) microfluidic geometry was used to 3D-print the scaffold. These drug-loaded scaffolds reportedly displayed significant cytotoxicity on MKN-45 gastric cancer cells *in*

vitro, while maintaining the viability of non-tumour cells and showed remarkable anti-recurrence percentages in gastric cancer postoperative models. Such results demonstrated a highly promising value of these composite scaffolds for postoperative tumour treatment [172].

6. Future perspectives & final remarks

Several reviews and research articles have already focused on microfluidic-assisted manufacture of fibres for biomedical applications, unanimously highlighting this technology's advantages over other spinning methods, even over the more commonly used electrospinning. Parameter controllability/tunability, raw material and morphology versatility, mild conditions and wide applicability are some of the beneficial features which encourage composite fibre manufacture via microfluidics. Considering the current polymer materials, even optimally developed fibres usually present meaningful challenges, particularly regarding the mechanical performance, biodegradability or bioactivity. Composite fibres enable to overcome these individual limitations and form hybrid fibres with synergistically enhanced features. Using microfluidic spinning approaches to construct composite fibres can therefore pave the way for a whole new host of biomedical applications in the foreseeable future.

Although microfluidic spinning is a relatively novel platform, its advantageous manufacture profile would suggest more active research efforts in the current biomedical research landscape. This underwhelming status stems from several challenges which, if surmounted, would promote microfluidic synthesis of composite fibres as a key platform in biomedical science. Firstly, to overcome the current lack or inadequacy of raw materials, the growing research and development in composite fibres and novel suitable materials stands out as a promising solution, as composites will continue to display unprecedented enhancements both in mechanical as well as in functional features [5,81]. Biomedical applications of fibrous materials will therefore expand even further with composite fibres. Particularly, we encourage a deviation from (non-composite) ionically cross-linked alginate fibres, the most widely fabricated fibre via MST, since they consistently display some limitations. Secondly, the translation of this technology from an academic setting to an industrial/clinical application is limited by its onerous mass production of chips [224]. Parallelization scale-up is a common strategy to achieve products in the order of kilograms [61,85], however, to obtain high-throughput manufacture, novel microfluidic chips should be developed. In this regard, emerging 3D technologies can be a highly suitable approach for single-step fabrication of microfluidic chips with defined cross sections and complex structures [106,239]. The development of integrated microfluidic devices, with sequential production-modification-purification or with *in situ* monitoring, is also a promising tool to manufacture increasingly complex fibres [11]. Thirdly, microfluidic technology must cease to be

viewed simply as an alternative production method. MST, as presented in this review, enables a degree of process tunability and versatility which only electrospinning comes close to. Additionally, the combination with other spinning techniques (namely, electrospinning and solution blow spinning) could extend even further its manufacturing possibilities.

In summary, the development of microfluidic technology for composite fibre manufacture opens exciting new possibilities to expand current biomedical applications, such as tissue engineering, wound healing and drug delivery. Nonetheless, we point out that the microfluidic approach must not be regarded as unequivocally enabling in all contexts [228]. We also underline the need for further investigations and optimizations, since this technology is still taking its first steps towards a future with feasible mass production of high-value composite fibres with increasingly advanced functionalities (for instance, smart sutures [240]), which will undoubtedly lead to a paradigm shift in healthcare.

TABLE 2

Spinning Technique	Driving force	Critical Process Parameters	Fibre Morphology	Advantages	Limitations
Dry spinning	High pressure	Polymeric fluid (composition, concentration); Equipment (spinneret shape, spinning and drafting speed); Environment (temperature, humidity); post-processing	Single fibre with different morphologies	Fast and efficient, less-emission, the shorter process and smaller diameter fibres than wet spinning	Harsh technology, requirement for recycling solvent and higher cost, lower spinning speed than melt spinning, less spinneret holes than wet spinning
Wet spinning	High pressure	Polymeric fluid (composition, concentration); Coagulation bath; Equipment (spinneret shape, spinning and drafting speed); Environment (temperature, humidity)	Skin-core structure	Fast and efficient; Low-precision requirement, more holes in spinnerets than melt spinning; Wide commercial use	Complex process, low speed, requirement for cleaning, surface grooves are not always distributed along the axial direction, higher cost than dry-jet and wet spinning
Dry and wet spinning	High pressure	Polymeric fluid (composition, concentration); Coagulation bath; Equipment (spinneret shape, spinning and drafting speed); Environment (temperature, humidity)	Single fibre with different morphologies	Fast and efficient; nearly circular fibre cross-section; low solution recovery and less wastage	Separation properties, Young modulus and tensile strength slightly inferior to wet spinning, larger fibre diameter
Melt spinning	High pressure	Polymers (molecular weight and distribution, degradation properties, purity); Equipment (process temperature, hot air pressure, receiving distance, spinneret shape,	Multicomponent, core-sheath structure, island type, orange petal structure	Fast and simple production line, low cost, environment-friendly, smooth fibre surface	Uneven fibre fineness and low mechanical strength, easily blocked spinneret holes

		spinning and drafting speed); Environment (temperature, humidity)			
Electrospinning	Electrostatic field force	Polymeric fluid (concentration, volatility, surface tension, viscosity, conductivity); Equipment (voltage, spinneret shape, tip-collector distance, spinning speed); Environment (temperature, humidity)	Diverse structures with possible alignment (solid, beaded, hollow, hybrid, core-shell, flat, porous, etc.)	Simple operation; high density; wide selection of materials; simple device; generation of submicron-nanometre fibres; can produce three-dimensional structures	Poor control of fibre morphology, power consumption, environmentally sensitive; toxic solvent volatilization/residue (solution), polymer needs to have some electrical conductivity and thermal stability (melt), random fibre deposition
Microfluidic spinning	Micro/Nanoscale fluid dynamics	Polymeric fluid (concentration, surface tension, viscosity); Equipment (flow rate and channel configuration; cross-linking method	High structure flexibility (core-sheath, hollow, porous, spiral and patterned/coding structures)	Precise and flexible control of fibre parameters, high reproducibility, feasibility of 3D structures; mild process conditions; tuneable porosity; Cell incorporation; Nano/microfibres (hundreds of 10^{-9} m to 10^{-6} m)	Low speed (10^{-2}m/s) and mechanical strength (hydrogels)

Table 2 - Comparison between the currently available and relevant spinning methods for fibre manufacture, including conventional (dry spinning, wet spinning, dry-jet wet spinning, melt spinning) and emerging methods (microfluidic spinning and electrospinning) [28,35].

7. Declaration of Competing Interest

Rodrigo Dores, Mónica S.N. Oliveira and Luis M. Bimbo have no known competing financial interests or personal relationships that could, or appear to, influence the work reported in this paper.

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