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Hydrogels Fibers

Javad Foroughi, Azadeh Mirabedini and
Holly Warren

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Abstract

With the ever increasing demand for suitable tissue engineering and drug delivery systems, hydrogel fiber spinning has drawn increasing attention due to its ability to create three-dimensional (3D) structures using biomaterials. Hydrogel materials have shown a great promise to be used as templates for tissue engineering and implantable devices. Among the many production techniques available, advanced fiber processing, such as coaxial and triaxial spinning of natural hydrogels, has attracted a great deal of attention because the basic core-sheath structure provides a drug delivery system capable of delivering high concentrations of drug for localized drug delivery and tissue engineering applications. Encapsulating the drug and bioactive cores with a more bio-friendly coating allows for a versatile system for producing devices with appropriate mechanical, chemical and biological properties that can mimic the native extracellular matrix, better supporting cell growth and maintenance. This chapter presents a novel fabrication method using a wet-spinning process that allows for the routine production of multifunctional coaxial hydrogel fibers that take advantage of the encapsulating properties of a hydrogel core while also promoting good cell growth and biocompatibility via the use of bio-friendly material in the sheath.

Keywords: fiber, biomaterial, hydrogels, biomedical applications, drug delivery

1. Introduction

1.1. Material considerations for biomedical applications

For an ideal scaffolding material, properties are required that include biocompatibility, suitable microstructure, desired mechanical strength and degradation rate as well as, most importantly, the ability to support cell residence and allow retention of metabolic functions. Various approaches to engineer tissues currently exist and rely on the implementation of a material scaffold. These

structural scaffolds aim to serve as a synthetic extracellular matrix (ECM) to both guide cell growth in a controlled 3D pattern and directly apply certain stimuli which promotes this growth. These scaffolds and stimuli are tailored for specific tissue growth and applications and therefore can vary greatly. A wide range of materials are known to be utilized as cell supporting materials in biomedical applications including natural and synthetic polymers, metals, ceramics and alloys [1]. Aside from the specific materials used in certain applications such as orthopedics, dental implants and artificial vascular materials, the focus of this chapter is on the role of naturally occurring hydrogels to develop biofibres with the final use as biocompatible templates for the purpose of drug delivery systems or the building blocks of tissue scaffolds. Herein, hydrogels including alginate and chitosan are introduced and explained as follows.

1.2. Natural hydrogels

Natural polymers can be considered as the most commonly used clinical biomaterials. Polymers of natural origin are attractive options, mainly due to their similarities with ECM as well as their chemical versatility and biological performance [2, 3]. A variety of hydrogels [4, 5] have been investigated as potential tissue scaffold materials. Hydrogels are three-dimensional, covalently crosslinked polymer networks with a high number of hydrophilic groups, capable of accommodating large amounts of water. Their hydrophilic polymer chains are either synthetic or naturally sourced and can exhibit tunable mechanical properties depending on their cross-linking mechanisms. Hydrogels used in bioapplications are typically degradable, can be processed under relatively mild conditions, have mechanical and structural properties similar to many tissues and the ECM, and can be delivered in a minimally invasive manner.

Hydrogels demonstrated a distinct efficacy as matrices for 3D cell culture since they are mechanically similar to living tissues and ECM, such as a soft and rubbery yet deformable nature, with low interfacial tension with biological fluids [6]. In addition, they can use biologically relevant electrolytes which makes them well suited for applications within biology [7]. Another unique characteristic of biomimetic hydrogels is that they may undergo huge volume changes, which occur in relatively narrow ranges of changes of temperature, pH, and ionic strength [8].

Polysaccharides are a typical group of natural biopolymers showing great swellability that make them ideal candidates for preparing hydrogels. Polysaccharides are high molecular weight polymeric carbohydrates formed from repeating monosaccharide units [1]. Polysaccharides are advantageous for biomedical applications due to their wide availability, low cost as well as the presence of functional groups in the polymer chain. They offer a wide diversity in structure and properties due to their wide range of molecular weight and chemical composition. Alginate and chitosan are considered as the most extensively used gel-forming polysaccharides for cell growth from natural sources. They were chosen and used in this study mainly due to their several unique properties including biodegradability, biocompatibility, low toxicity, promoting attachment, migration, proliferation and differentiation of cells and antimicrobial activity as well as ease of fabrication and availability [1].

1.3. Sodium alginate

Alginate, or alginic acid, is an anionic polysaccharide extracted from brown algae and seaweeds. Discovered by Stanford in 1881, it is a common food additive but also used in

pharmaceuticals, textile printing and for many other applications. Alginate is a linear, binary copolymer composed of 1, 4-linked β -D-mannuronic acid (M) and α -L-guluronic acid (G) monomers. Alginates are extracted from algae using a basic solution [9]. The extracted material is then reacted with acid to form alginic acid. The composition of alginate (the ratio of the two uronic acids and their sequential arrangements) varies with the source. Salts of alginic acid with monovalent cations such as sodium alginate are all soluble in water and capable of holding a large amount of water. Alginate has been extensively used as a scaffold for liver, bone, nerve and cartilage engineering [1]. Even though, alginates are non-toxic and biocompatible, using them for biomedical applications has several drawbacks. Alginates are mechanically very weak in their swollen state, therefore it should be blended or modified or copolymerized with other biopolymers before being used as a structural scaffold. More importantly it shows poor cellular adhesion. The chemical structure of sodium alginate is demonstrated in **Figure 1**.

By forming alginate into fibers, novel biomaterials are attainable which can be processed further into woven, non-woven, braided, knitted and many other kinds of composite structures. In the wet-spinning process in which alginate is transformed from powder into a fibrillar-shape, alginate powder is needed to be dissolved in water and stirred properly to form a homogenous solution first. The final properties of wet-spun alginate fibers highly depend on a number of factors, such as chemical structure and molecular weight of the alginate, composition of the coagulation bath, drawing ratio, temperature and feeding rates, etc. The spinning solution is one of the first main considerations in the wet-spinning process which determines the production efficiency. The fiber final performances strongly depends on several parameters including concentration, temperature and pH of the spinning solution [10]. A concentrated sodium alginate solution can be extruded through spinneret holes into a calcium chloride (CaCl_2) bath, whereby the high acid content allows alginic acid to undergo spontaneous and mild gelling in the presence of di- or trivalent cations. Thus, it is possible to use a variety of metal ions such as zinc, silver or other bioactive metal ions to precipitate sodium alginate solution during the wet-spinning process as tried previously [11]. Among divalent ions, calcium has found greatest popularity for gel formation of alginate fibers mainly because its salts are cheap, readily accessible and cytocompatible. Since processing takes place in an aqueous solution and in an aqueous coagulation bath at a neutral pH, many bioactive materials, such as drugs and enzymes, can be combined into the alginate fibers, without loss of their bioactivity. On the other hand, calcium alginate fibers have proven to be unstable structures as tissue scaffolds or drug vehicles for in-vivo usages [11, 12].

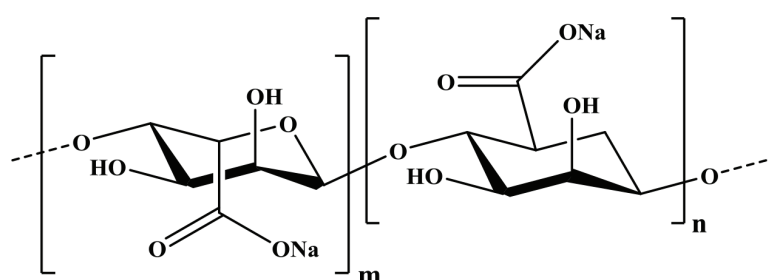


Figure 1. Chemical structure of sodium alginate.

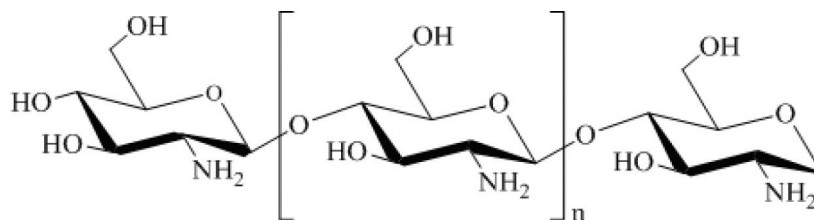


Figure 2. Chitosan chemical structures.

1.4. Chitosan

Chitosan is a semi-crystalline natural polysaccharide [1] with a totally different nature than that of alginate which has recently generated great interest for its potential in clinical and biological applications such as artificial skin, tissue engineering and controlled drug delivery. The cationic polymer chitosan originates from crustacean skeletons [13]. Structurally, chitosan is a semi-synthetically derived aminopolysaccharide which is the N-deacetylated product of chitin, i.e. poly-(1 \rightarrow 4)-2-amino-2-deoxy- β -D-glucose [1]. Chitosan shows an enhanced hydrophilicity compared to that of chitin which results in a considerable loss of tensile strength in the wet state. This hydrogel is highly reactive due to free amine groups and is readily soluble in weakly acidic solutions resulting in the formation of a cationic polymer of chitosan acetate with a high charge density. These solutions generally have high solution viscosities due to the phenomenon known as the polyelectrolyte effect [14]. Porous chitosan matrix has been used as a scaffold for skin, liver, bone and cartilage, cardiac, corneal and vascular regenerative tissue remodeling. It has also been applied in controlled drug delivery in different shapes such as spheres, films or fibers. The chemical structure of chitosan is shown in **Figure 2**.

Chitosan can be produced in a variety of forms including films, fibers, nanoparticles and microspheres. There have been many attempts by several groups into aqueous basic coagulating baths to produce chitosan fiber [1, 11, 15]. For the purpose of wet-spinning, the chitosan solution is generally extruded into an alkaline solution such as aqueous NaOH as the coagulation bath which forms the fibers. The coagulation rate, which also includes the regeneration of the free amine form of chitosan, is also expected to be influenced by high solution viscosity. Nevertheless, the strong alkaline condition (pH > 12) needed to form chitosan-based structures, can limit its utilization for loading most of drugs or bioactive molecules into it.

2. Fabrication methods

2.1. Wet-spinning

The number of fabrication methods for developing three-dimensional structures to be utilized for biological applications have risen due to the inability of two dimensional structures to mimic the extracellular matrix accurately. To design a three-dimensional architecture which imitates the ECM, several parameters such as geometry, mechanical and surface properties as well as biocompatibility are required to be taken into account. Fibers spinning [16] has been used to produce synthetic fibers by first dissolving the desired polymer in a suitable solvent

and directly extruding it into a coagulation bath. The bath must contain a liquid which is miscible with the spinning solvent but a non-solvent of the polymer, hence, the solvent is removed from the polymer, leaving a solid fiber which precipitates out of the solution.

Wet-spinning is usually subdivided into three main steps based on different spinning strategies as follows; (a) phase separation, (b) gel separation and (c) liquid crystal spinning. During the phase separation, rapid formation of the fiber structure will occur as a result of polymer solution exposure with the coagulation bath. As the polymer fluid is injected into the non-solvent, the solvent is extracted from the polymer solution causing the polymer to be precipitated in the bath to form a semi-solid fiber. Further solidification into a coagulation bath provides sufficient cohesion and strength for the fiber to be continuously collected when coming out of the coagulation bath. In the second step, the polymer is coagulated due to intermolecular bonds such as ionic cross-linking by a salt or another reacting agent. In the liquid crystal spinning stage, lyotropic crystalline solution provides sufficient alignment and cohesiveness to form a solid crystalline phase for fibers. A schematic of wet-spinning is shown in **Figure 3**. Although coaxial electrospinning was used by many researchers to produce coaxial fibers, only a few reports which appeared in the literature reported the successful fabrication of hybrid fibers *via* coaxial wet-spinning methodology to the knowledge of author. This might be due to the complexity of this method because of plurality of parameters involved in the successful formation of a core-sheath structure inside a coagulation bath. In the first instance, the fabrication of wet-spun coaxial fibers appears a straightforward task; two different components are injected through a coaxial spinneret at once into a proper coagulation bath to form a coaxial structure. However, this simple approach presents several challenges. Many parameters are needed to be controlled and regulated in order to hold both components in a coaxial structure. Among those, the solution properties are known as the key factors affecting the spinning process including mainly the material concentrations, viscosities, surface charges, surface tensions, polymer natures and functionalities and so on. However, less important considerations such as systematic variables (injection rates (V_i), core to sheath injection rates ratio, take-up velocity (V_t), coagulation bath constituents, drawing velocity (V_d), spinneret specialties, post-treatment processes, etc.) and ambient conditions (temperature, post-

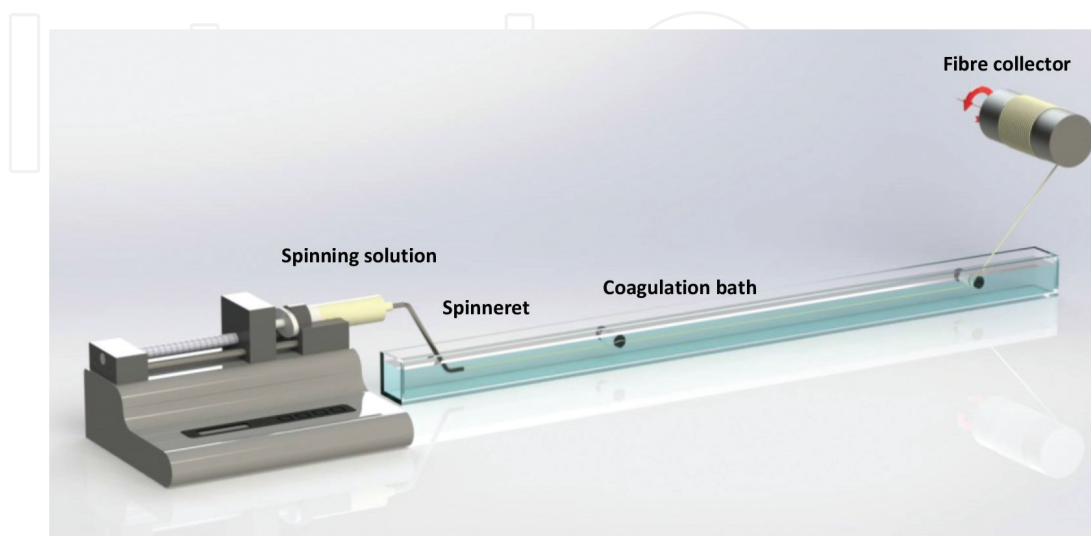


Figure 3. Schematic of a Lab scale wet-spinning line.

spinning conditions) could be also influencing the process as well as final fiber properties significantly. Up to date, different examples of coaxial fibers have been reported using a number of materials such as conducting polymers, metals, natural polymers and carbon-based components *via* various production methods. Most efforts have been focussed on approaches based on electrospinning to date to produce coaxial structures. Some of the main techniques to produce coaxial fibers and yarns are described in the following sections. However, among earlier efforts to produce wet-spun coaxial fibers, few methods could be found sharing similar procedures to that of coaxial wet-spinning described below [16].

2.2. Production of hollow fibers

Many different types of semipermeable hollow fibers have been prepared by means of the melt, dry or wet-spinning techniques [1]. The procedure of achieving a hollow structure is quite similar to that of coaxial wet-spinning in which the sheath spinning solution was delivered from a chamber to the external spinneret nozzle through injection, whereas the core fluid is usually substituted simply with pressurized water or the coagulant fluid injected to the central nozzle. These fibers are being applied in various purposes such as gas separation, ultrafiltration, reverse osmosis as well as many biological applications including drug delivery, dialysis and tissue engineering.

Delivery systems with diverse release profiles spanning from a few days to several months have been achieved by encapsulation of biological molecules as well as drug reservoirs into the core of hollow fibers or chemically cross-linking or adsorbing therapeutics to the surfaces of fibers. With regard to the encapsulation of drugs within wet-spun filaments, a critical issue is obtaining the appropriate release characteristics and mechanical integrity for specific cell type/tissue architecture. The fabrication of the hollow PLGA fiber has been done as a controlled drug release system [15]. A method also *has* been described for encapsulation of human hepatocellular carcinoma cells in wet-spun chitosan-alginate microfibres [1]. In addition to those mentioned, many other research groups reported on using a hollow fiber structure for delivering biomolecules [1, 11, 15].

2.3. Coaxial wet-spinning

Despite those preliminary studies to produce fibers with similar structures to that of the coaxial fibers such as hollow and core-skin fibers mentioned previously [3], there are only a few reports in the literature of fabrication of coaxial fibers using a coaxial spinneret for wet-spinning. The major difference of conventional wet-spinning with the coaxial method is that in the coaxial process, two different polymer solutions are injected into a coaxial spinneret together and are co-extruded into a bath while retaining a coaxial structure. A schematic of coaxial wet-spinning setup is shown in **Figure 4**.

Coaxial wet-spinning produces hollow or core-shell fibers that can be used for quite a lot of purposes such as controlled release applications, electronic textiles, sensors and actuators [12]. As a matter of fact, for the successful production of coaxial fibers, several parameters are needed to be controlled and regulated. Thus, development of a simple yet effective wet-

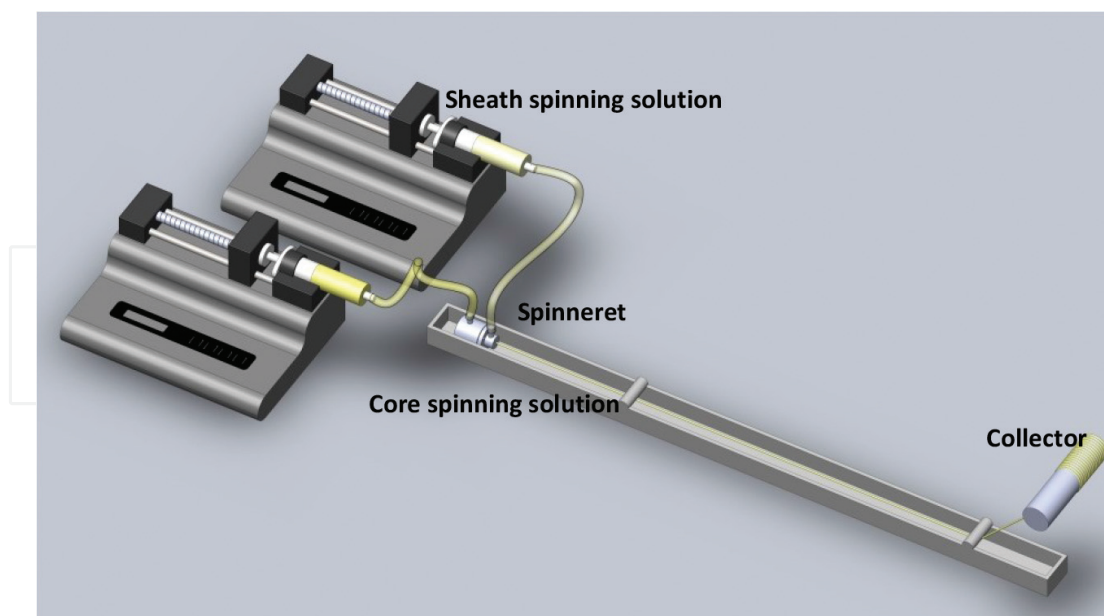


Figure 4. Coaxial wet-spinning setup.

spinning approach for direct preparation of sheath-protected fiber electrodes still remains a challenge. Among those, solution properties are of great importance such as material concentrations, viscosities, surface charges, surface tensions, polymer natures and functionalities etc. However, process parameters could also influence the process as well as the final fiber properties significantly. G. Park and his co-workers were successful to spin CNT/Poly (vinyl alcohol) fibers with a sheath-core structure *via* wet-spinning [1]. Recently, Liang Kou *et al.* have also reported on the production of CMC/wrapped graphene/CNT coaxial fibers for supercapacitor applications [15].

3. Materials and methods

3.1. Wet-spinning of hydrogels fibers

Wet-spun chitosan fibers were produced in a coagulation bath consisting of 1 M sodium hydroxide (NaOH) using a rotary wet-spinning system. Uniform alginate fibers were spun in a 2% CaCl₂ coagulation bath. Core-sheath fibers of chitosan-alginate (Chit-Alg) were successfully spun using a coaxial spinneret. The chitosan spinning solution (with different amounts of CaCl₂) was injected as the core component and extruded through the center nozzle into the coagulation bath of calcium chloride [11]. Simultaneously, alginate was injected as sheath of the fiber, providing an outer casing for the core, by injection through port A. In this method, by using a blend of chitosan with various percentages of calcium chloride, it is possible that the alginate sheath can be coagulated from the inner chitosan core, while also creating the opportunity to react chitosan with sodium alginate at a much faster rate [1]. The setup is shown in **Figure 4**, previously. Therefore, as mentioned earlier chitosan solutions including 0.5, 1 and 2% (w v⁻¹) CaCl₂ were prepared for the core component of the fibers and alginate sheath. The

samples are named here as Chit-Alg (0.5), Chit-Alg (1) and Chit-Alg (2). Solutions were delivered at flow rates of 14 mL h^{-1} for chitosan and 25 mL h^{-1} for the sheath [11].

Toluidine blue (TB) was used as an indicative dye incorporated into the coaxial fibers to track the release experiment. For the purpose of fiber preparation for release experiments, the dye was mixed with chitosan solution before spinning with the concentration of 0.1% (w v^{-1}) and then injected as the core component. These solutions were then spun into the same coagulation baths which were previously used to make pristine fibers. Coaxial fibers containing TB were also fabricated using the method mentioned previously with the small difference of using chitosan/TB solution as the core component [11].

3.2. Toluidine blue release measurement

The release kinetics of the prepared fibers for drug release applications was studied using TB as a model dye introduced into the fibers over a 5-day period. The amount of released TB was determined *via* UV-vis spectroscopy by monitoring the absorption of TB at its λ_{max} 630 nm in simulated body fluid (SBF). To construct an absorbance calibration curve for sample analysis using a Shimadzu UV 1601 spectrophotometer, UV-vis spectra of SBF solutions containing TB with different concentrations were recorded between 200 nm and 1100 nm. Approximately 5 cm of each dried sample (in triplicate) was placed in a 2 mL Eppendorf tube and 1 mL of SBF was added into it. The release medium was taken by micro-pipette at specific time points over 5 days and replaced with the same volume of fresh SBF solution to maintain the total volume constant. The percentage of released TB (%) was plotted versus time [11].

4. Results and discussion

Initial investigations were aimed at determining the spinnability and the physical characteristics of potential dopes to ensure they were in the range required for fiber formation.

4.1. Spinnability vs. concentration

Spinnability can be defined as the ability of a material of being suitable for spinning or the capability of being spun. In the context of wet-spinning, spinnability could be referred to the ability of a solution to form fibrillar arrangements *via* injection into a non-solvent medium which makes it precipitate, so-called a coagulation bath [16]. The spinnability of a polymer solution depends on many parameters, including the rheological properties of a solution, size of nozzle, shear rate applied during injection through spinneret and mass transfer rate difference between the extruded solution and non-solvent. Several types of either suitable solvent or coagulant could be employed depending on the chemical structure of material. Often an upper and lower limit for polymer concentration during wet-spinning is considered facilitates spinning continuous length of fibers. The capillary break-up is widely understood as a surface-tension induced break-up of filaments into drops can occur at low concentrations of the polymer solution which determines the lower limit of spinnability. Spinnable concentrations

have been reported for chitosan varying from 2 to 15% ($w v^{-1}$). Here, we found that 2–5% ($w v^{-1}$) is the appropriate concentration range enabling wet-spinning of MMW chitosan into a coagulation bath of 1 M NaOH. Observations also indicated that aqueous alginate solutions at a concentration of below 2% ($w v^{-1}$) would not generate a continuous fibrous structure *via* wet-spinning; increasing the alginate concentration from 2 to 4% ($w v^{-1}$), the solution became highly spinnable [1]. Then again, at concentrations above 4% ($w v^{-1}$), the solution became highly viscous which impeded continuous flow through the needle, rendering the solution unspinnable. A concentration of 3% ($w v^{-1}$) has been thus selected for both gel precursors due to the ease of spinnability, together with maintaining the suitable mechanical properties for coaxial wet-spinning [1].

4.2. Rheology

Viscosity is considered in the selection of suitable concentrations of chitosan and alginate solutions for fiber spinning. For coaxial spinning matching viscosities of the two components is also a consideration [1]. **Figure 5** shows changes in viscosity versus shear rate was determined from aqueous solutions of chitosan at 3% ($w v^{-1}$) and alginate at 3% ($w v^{-1}$). Spinning solutions of 3% ($w v^{-1}$) chitosan resulted in a solution with a viscosity of 6.4 Pa·s. The viscosity of 3% ($w v^{-1}$) sodium alginate solution was approximately 8.5 Pa·s. The viscosities of the two solutions became closer as the shear rate increased. Under shear, hydrogel chains are in a less expanded conformation and become less entangled causing the viscosity to drop. At the time of spinning, chitosan is injected with rate of 14 mL h^{-1} while is 25 mL h^{-1} for the alginate solution. The shear rates calculated to be about $\sim 97 s^{-1}$ for alginate and $\sim 75 s^{-1}$ for chitosan

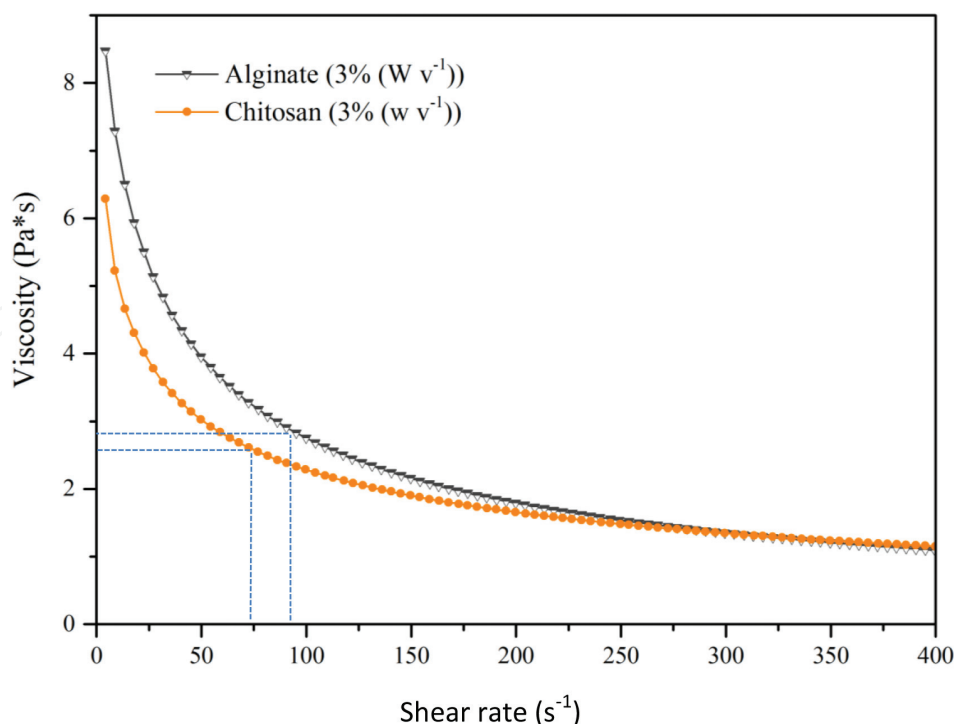


Figure 5. Viscosities of spinning solutions of chitosan and sodium alginate [11]. Reproduced with permission. 158 Copyright 2015, Wiley-VCH.

solutions which resulted in a viscosity of ~ 2.5 Pa·s for chitosan and ~ 2.8 Pa·s for alginate solutions. These outcomes seem to be ideal for coaxial spinning [1].

4.3. Continuous spinning of coaxial fibers

To produce continuous uniform fibers, chitosan with injection rate of 14 mL h^{-1} and alginate solution with rate of 25 mL h^{-1} have been simultaneously injected into the 2% (w v⁻¹) aqueous CaCl_2 coagulation bath through the ports built in the coaxial spinneret [11]. Using this method, an unlimited length of fibers could be obtained which was collected using a collector as shown in **Figure 6**. It is worth mention that the preparation of coaxial fibers without incorporating a certain amount of CaCl_2 did not turn out to be successful when tried.

The woven structure of Chit-Alg fibers (containing TB) in dry and wet state were shown in **Figure 7 (a)** and **(b)**, respectively. This capability provides the potential for these structures to be utilized as tissue scaffolds and drug delivery vehicle applications [11].

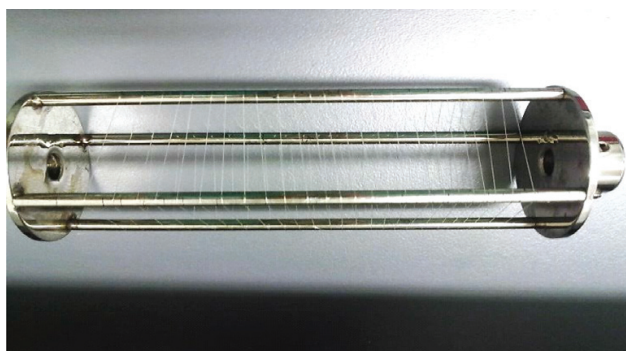


Figure 6. The capability of producing unlimited length of coaxial Chit-Alg (1) fibers as shown onto a collector. [11] Reproduced with permission. 158 Copyright 2015, Wiley-VCH.

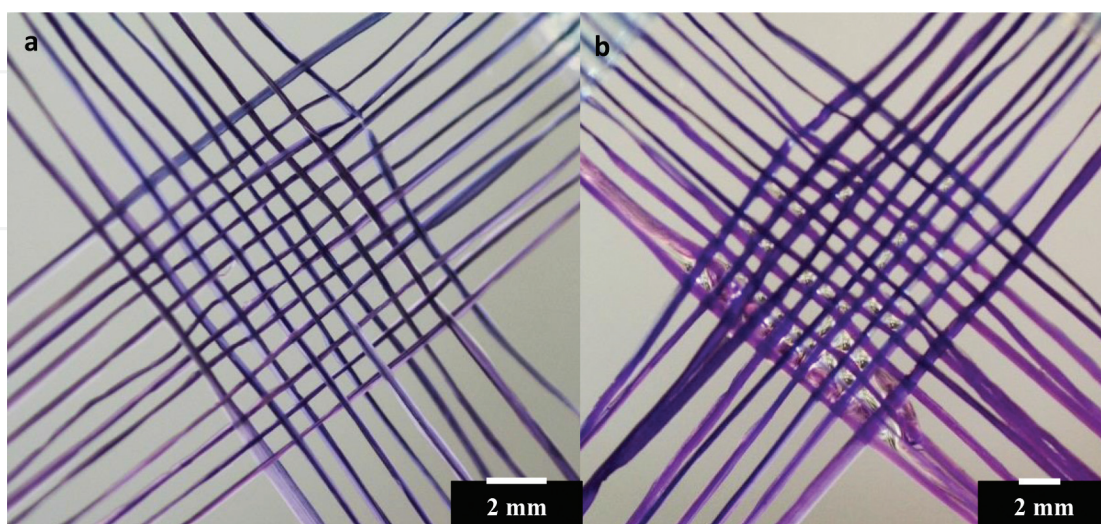


Figure 7. The photographs of scaffold structure woven by coaxial fibers; imaged in (a) dry state and (b) wet state. [11] Reproduced with permission. 158 Copyright 2015, Wiley-VCH.

4.4. Morphology of As-prepared fibers

The stereomicroscope images of wet-spun chitosan, alginate and core-sheath Chit/Alg fibers are shown in **Figure 8** in wet and dry-states.

As can be seen in **Figure 8 (a)** and **(b)**, the surface of the chitosan fiber seemed to be very smooth and soft, while some wrinkles can be noticed spreading on the surface of the alginate fiber which will be increased during the fiber drying process [1]. Moreover, one can see that the

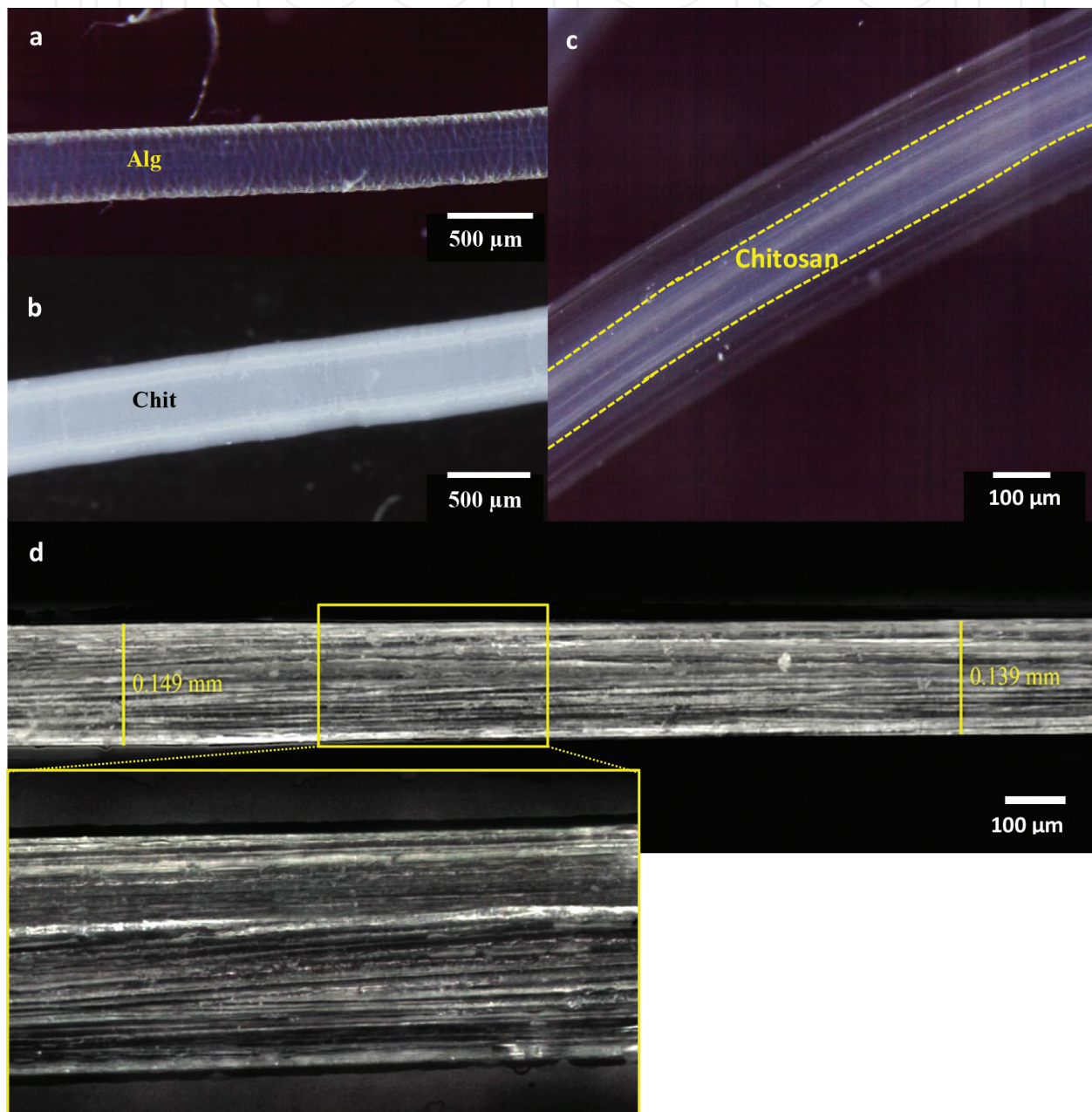


Figure 8. Stereomicroscope images of side view of wet (a) alginate, (b) chitosan, (c) coaxial Chit-Alg (1) and (d) dry Chit-Alg (1) fiber. [11] Reproduced with permission. 158 Copyright 2015, Wiley-VCH.

core-sheath fibers are straight and smooth with a core loaded in the center of fibers. They have a uniform structure and diameter of ca. 220 μm and 136 μm for the sheath and core when wet, respectively (**Figure 8(c)**). However, the dried fibers hold the thickness of $\sim 140 \pm 10 \mu\text{m}$ (This average value was calculated after measuring the diameter under the stereomicroscope 10 times). In addition, some lines or longitudinal indentations can be observed running parallel with the fibers on totally dried core-sheath fiber as shown in **Figure 8 (d)**. The chitosan core is $\sim 90 \mu\text{m}$ which is surrounded by a thin layer of alginate sheath of $\sim 8\text{--}12 \mu\text{m}$. Still, the thicknesses of core and sheath materials are adjustable by changing solution feed rates and the drawing ratio (data, variables *vs.* dimensions). Considering two selected collection rates at angular velocities of 20 and 60 rpm (with the assumption of keeping the injection rates constant), it is possible to measure draw ratio upon increasing the collection rate from 20 to 60 rpm while having a constant collector [1].

The fiber diameter decreased as the drawing ratio increased. In general, the molecular orientation of fiber materials obtained through the drawing process governs their properties, particularly the mechanical properties. In addition, the thickness of the sheath would have a direct relationship with increasing its injection rate; the thickness of alginate increased as the shear rate increased while the feeding rate of core component was kept constant. However, while the application of shear is essential in obtaining orientation in the fiber, high shear rates develop beaded non-uniform fiber in the coagulation bath as a result of die swell (swelling of the free jet of solution upon injection from spinneret) and skin formation. Die swell occurs as a consequence of polymer relaxation due to its low entropy conformation after shear is applied during extrusion through the spinneret, where polymer molecules are oriented by the flow. The diameter of the jet then decreases as a result of drawing along the spinning path. A hard skin is also formed on the surface of the filament which results in the rate the jet diameter decreases. When the shear rate of chitosan increased to 20 mL h^{-1} , formation of the coaxial structure did not turn out to be successful. It seemed that the sheath components were not thick enough to hold the core material in place.

SEM images of cross-sections and the surfaces of solid and core-sheath fibers are illustrated in **Figure 9 (a–e)**. They give valuable information about the morphology of the two polymers. Before imaging fibers were immersed in SBF and imaged with SEM in an attempt to capture structural information in the “wet state”, since that is how they would be used in future possible applications [1].

Cross-sections of solid fibers fabricated showed the cylindrical shaped form of the hydrated chitosan and alginate solid fibers (**Figure 9 (a)** and **(b)**), respectively. Alginate fibers appeared to be permeable and spongy, while the cross-section of chitosan fibers appeared to be denser. In contrast, cross-sections of the coaxial fibers reveal slightly irregular, oval shaped fibers with a distinct separation between chitosan in the core and the outer alginate sheath as is indicated in **Figure 9(c)**. In addition, both polymers showed an extensive porous structure in the coaxial structure. On the cross-section of chitosan, regular crystalline structures can be seen which are probably due to the presence of calcium chloride inside the core (**Figure 9 (d)**), while alginate has a honeycomb structure (**Figure 9 (e)**). It is evident that the fiber is composed of two distinct areas of chitosan and alginate [1].

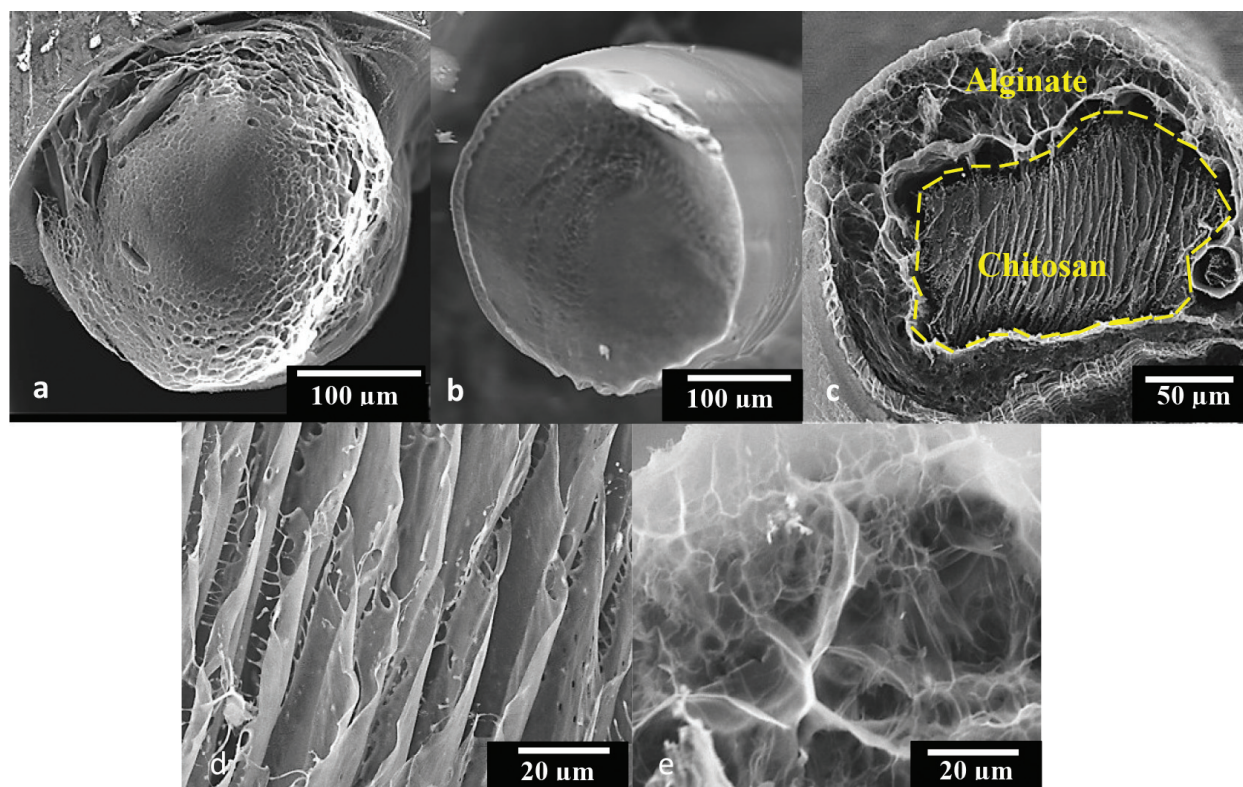


Figure 9. LV-SEM images of hydrated as-prepared (a) alginate, (b) chitosan and (c) Chit-Alg (1) cross-section in SBF, (d) chitosan core arrangement in cross-section (e) alginate sheath construction in the cross-section. [11] Reproduced with permission. 158 Copyright 2015, Wiley-VCH.

4.5. Mechanical properties of as-prepared fibers

The mechanical properties of alginate, chitosan and Chit-Alg coaxial fibers employing different concentrations of calcium chloride in chitosan core spinning dope are depicted in **Figure 10**. Ultimate stresses (MPa), ultimate strains (%), Young's moduli (MPa) and swelling ratios (%) were measured for alginate, chitosan, Chit-Alg (0.5), Chit-Alg (1) and Chit-Alg (2) fibers, respectively [11].

Mechanical analysis results revealed that with addition of more calcium chloride to the core-dope, the Young's modulus decreased. Increasing the amount of calcium chloride into fiber core will probably cause agglomerations which can lead to phase separation. Thus, there would be an upper threshold for the amount of CaCl_2 in the core at which the optimum mechanical parameters could be achieved. As a result, the mechanical properties of as-prepared fibers such as Young's modulus and ultimate stress were decreased by addition of more than 1% (w v^{-1}) CaCl_2 .

The results, which are presented in **Table 1**, also confirmed the reinforcing role played by the chitosan core in coaxial Chit-Alg fibers. Young's modulus was measured to be *ca.* 1.7 and 6.6 MPa for alginate and chitosan solid fibers, respectively. It has been also revealed that the fibers which contain 1% (w v^{-1}) CaCl_2 resulted in the highest mechanical results due to their modulus and ultimate stress compared to other coaxial fibers [11].

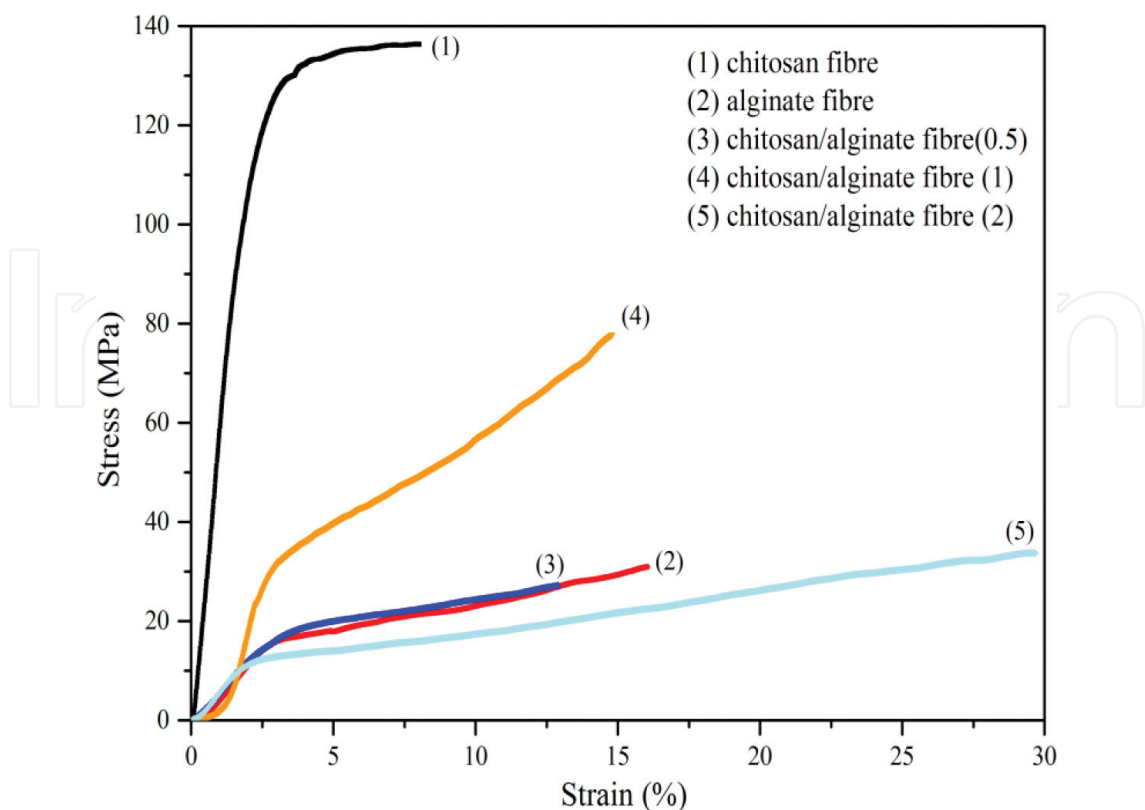


Figure 10. Stress-strain curves obtained from tensile tests of alginate single and chitosan/alginate coaxial fibers using different CaCl_2 concentrations. [11] Reproduced with permission. 158 Copyright 2015, Wiley-VCH.

Sample	Breaking stress (MPa)	Strain at break (%)	Young's modulus (GPa)	Initial swelling ratio (%)
Alginate fiber	$\sim 31 \pm 5$	$\sim 26 \pm 3$	1.6 ± 0.15	(Non-measurable)
Chitosan fiber	$\sim 146 \pm 30$	$\sim 19 \pm 5.2$	6.6 ± 0.8	~ 90
Chit-Alg (0.5)	$\sim 30 \pm 5$	$\sim 22 \pm 8$	0.6 ± 0.1	~ 360
Chit-Alg (1)	$\sim 80 \pm 10$	$\sim 14 \pm 3$	1.9 ± 0.2	~ 540
Chit-Alg (2)	$\sim 28 \pm 5$	$\sim 37 \pm 5$	0.55 ± 0.1	~ 385

Table 1. Comparison of mechanical properties of solid and coaxial biofibers [11]. Reproduced with permission. 158 Copyright 2015, Wiley-VCH.

4.6. Swelling properties in SBF

The swelling properties of the fibers were determined in SBF medium over a period of 48 hrs. Fiber diameters were measured at different time intervals. Results are shown in **Figure 11** and listed in **Table 1**. Solid fibers have shown quite different degrees of swelling; while chitosan fibers showed only 90% calcium alginate fiber, the swelling of alginate fibers occur quite fast up to high ratios (until the fiber lose its fibrillar shape completely which make it almost impossible to be measured). This phenomenon is mostly due to the ionic exchange between the divalent cations and sodium in the environment.

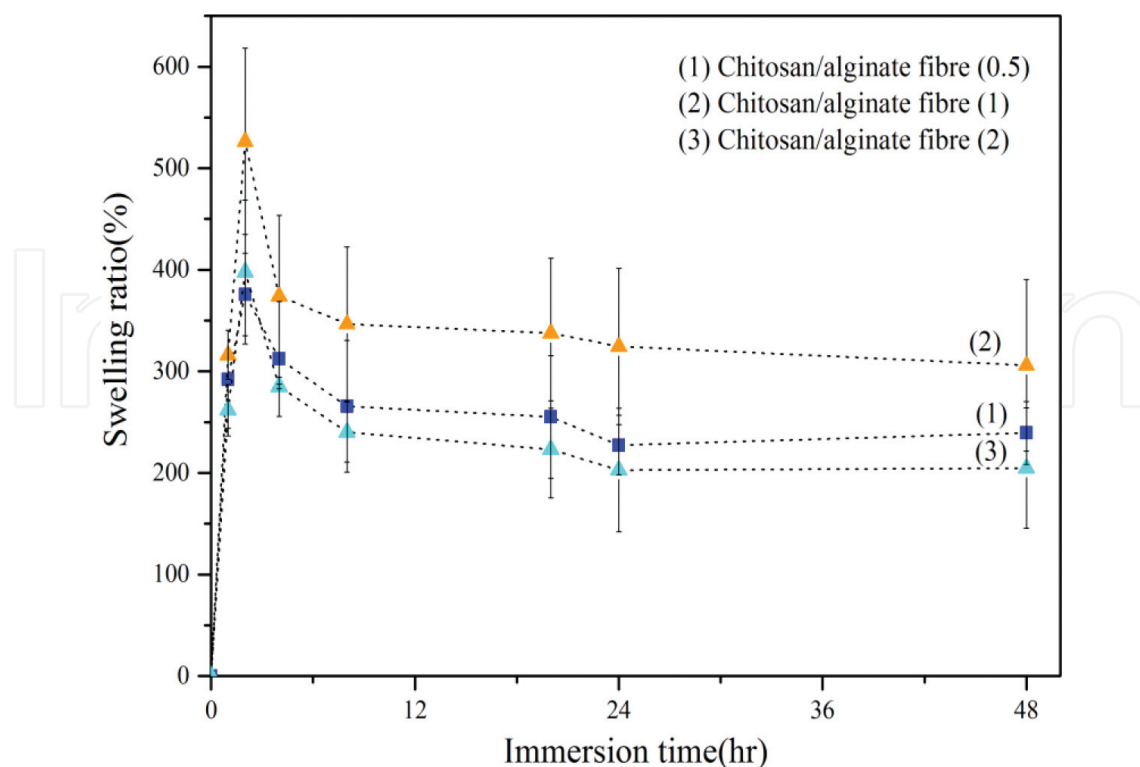


Figure 11. Swelling properties of coaxial wet-spun fibers in SBF as a function of the immersion time. [11] Reproduced with permission. 158 copyright 2015, Wiley-VCH.

It can be seen in **Figure 11** that coaxial fibers containing 0.5% ($w v^{-1}$) calcium chloride have shown the least amount of initial swelling, while fibers with 1% ($w v^{-1}$) calcium chloride in the core demonstrated the highest degree of swelling [1]. It seems that two simultaneous events are occurring by increasing the calcium chloride content in the core (from 0.5 to 2% ($w v^{-1}$)). Increasing the number of ionic groups (Ca^{2+}) in hydrogels is known to increase their swelling capacity [17]. This is mainly due to the simultaneous increase of the number of counterions inside the gel, which produces an additional osmotic pressure that swells the gel as described in Flory theory previously. Therefore, by adding more calcium chloride to the chitosan solution the degree of swelling increases. On the other hand, increasing the amount of Ca^{2+} ions also results in an increase in the ion exchange process within the sodium alginate. In fact, the ratio of calcium will increase in the alginate. The increase of the cross-linking agent concentration leads to the formation of a hydrogel with a greater 3D network density and so results in sheaths which show less swelling [1].

4.7. *In-vitro* release measurement

The calibration curve was determined by monitoring the absorption of TB at its λ_{max} (630 nm) in SBF with various concentrations of TB using UV-vis spectroscopy. The ability of the drug to release from the polymer matrix depend on a number of factors such as the solubility of the drug in the polymer matrix, the solubility of the drug in the medium, swelling and solubility of the polymer matrix in the medium and the diffusion of the drug from the polymer matrix to

the medium [18]. The release profiles of TB from dye loaded coaxial fibers in SBF for up to 5 days were plotted *vs.* time and are demonstrated in **Figure 12**.

The whole release time period varied for different types of fibers including alginate, chitosan and the core-sheath fiber depending on the period over which they could resist the media before their structure fell apart [1]. As noted previously, calcium alginate could be easily degraded when used for *in-vivo* applications due to the ionic exchange between the divalent cations and sodium in the which are present in the body environment [11, 18]. Therefore, it is believed that the release of TB observed from alginate fibers was mainly due to the degradation of alginate fibers. On the other hand, wet-spinning of chitosan fiber is needed to be done in basic coagulation bath which is not an appropriate condition for most of loaded drugs. Coaxial fibers indicated a controlled manner of release more or less like chitosan fibers. However, with the help of coaxial spinning, their fabrication process *via* wet-spinning is performed in a neutral coagulation bath. These results provide the suitable condition to load any types of drugs into the wet-spun fibers for drug delivery applications. As can be seen in **Figure 12**, the coaxial fibers showed similar release behavior to that of the chitosan fibers. However, they could withstand the media for a shorter period of time without losing the initial structure.

In the initial period of 2 h, a fast release of TB from alginate fibers is observed at which more than 70% of TB is released. Either chitosan or Chit/Alg coaxial fibers showed approximately 30% burst release of TB followed by a sustained release within over 5 days. While alginate fiber could not withstand the media for more than 4 days, *ca.* 42 and 50% of the TB is released from chitosan and Chit/Alg fibers, respectively. **Figure 12** shows a good sustained-release profile of

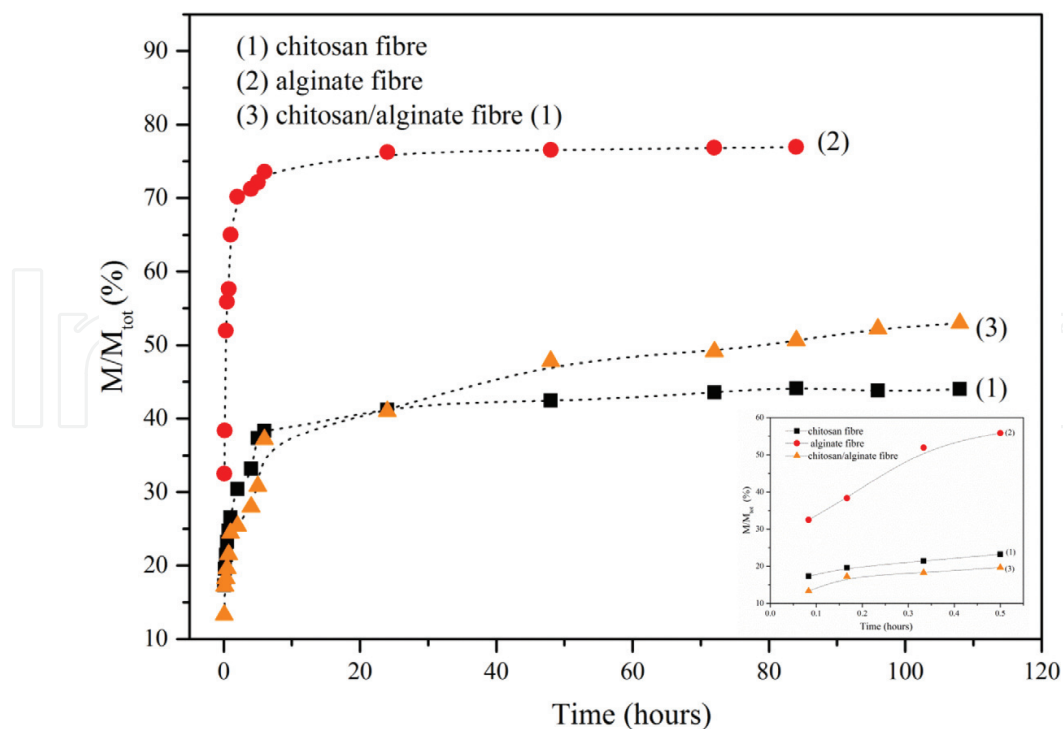


Figure 12. Time dependent TB releasing behavior of chitosan, alginate and Chit/Alg hydrogel fibers in SBF at 37°C. Inset; burst release of coaxial fibers in the first 30 min. [11] Reproduced with permission. 158 Copyright 2015, Wiley-VCH.

TB from coaxial fibers. TB is a hydrophilic molecule with a greater solubility in aqueous environment, so its drug diffusion rate through the polymeric matrix is highly dependent on the swelling of the polymeric fiber. Thus, according to the swelling ratio results, it is expected to obtain much faster release from alginate fibers than those of either chitosan or coaxial fibers [11].

5. Conclusion

The development and fabrication of hydrogels fibers has been carried out to evaluate their performance for drug delivery systems. The production of coaxial hydrogels fibers were successfully developed for the first time using a wet-spinning method. The morphological, mechanical, thermal and swelling properties of these fibers are discussed [1]. Enhanced mechanical properties of 260% in ultimate stress and more than 300% in the Young's modulus were observed by incorporating 1% (w v⁻¹) CaCl₂ into the chitosan core. SEM micrographs of the cross-section of chitosan-alginate fibers clearly show the cylinder shaped monofilament form of the chitosan fiber covered with alginate. These biofibers as delivery platforms have demonstrated great potentials toward advancing current drug delivery systems. Hybrid Chit/Alg fibers could likely be promising as a novel kind of 3D bioscaffolds in drug release studies or tissue engineering [1].

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Conflict of interest

The authors declare that there is no conflict of interest; this chapter is wholly our own work unless otherwise referenced or acknowledged. The document has not been submitted for publication at any other publishing organization.

Acronyms and Abbreviations

3D	three-dimensional
ECM	extracellular matrix
Chit	chitosan
Alg	alginate

CaCl ₂	calcium chloride
V _i	injection rate
TB	toluidine blue
SBF	simulated body fluid

Author details

Javad Foroughi*, Azadeh Mirabedini and Holly Warren

*Address all correspondence to: foroughi@uow.edu.au

Intelligent Polymer Research Institute, University of Wollongong, NSW, Australia

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