ELECTROSPUN SODIUM ALGINATE/POLY(ETHYLENE OXIDE) NANOFIBERS FOR WOUND HEALING APPLICATIONS: CHALLENGES AND FUTURE DIRECTIONS

HAFEDH AHMED AL-MOALEMI,[*] SAIFUL IZWAN ABD RAZAK[**] and SITI PAULIENA MOHD BOHARI[*,***]

[*]*Department of Bioscience, Faculty of Science, Universiti Teknologi Malaysia, 81310, Skudai, Johor, Malaysia*
[**]*BioInspired Device and Tissue Engineering Research Group, School of Biomedical Engineering and Health Sciences, Faculty of Engineering, Universiti Teknologi Malaysia, 81300, Skudai, Johor, Malaysia*
[***]*Cosmetic and Fragrance Laboratory, Institute of Bioproduct Development, Universiti Teknologi Malaysia, Johor, Malaysia*
✉ *Corresponding author: S. P. M. Bohari, pauliena@fbb.utm.my*

Received October 10, 2021

Alginate is an interesting natural biopolymer to be considered for biomedical applications due to its advantages and good biological properties. These biological properties make electrospun alginate nanofibers suitable for various uses in the biomedical field, such as wound healing dressings, drug delivery systems, or both. Unfortunately, the fabrication of alginate nanofibers by electrospinning is very challenging because of the high viscosity of the solution, high surface tension and rigidity in water due to hydrogen bonding, and also their diaxial linkages. This review presents an overview of the factors affecting the electrospinning process of sodium alginate/poly(ethylene oxide) (SA/PEO), the application of SA/PEO in drug delivery systems for wound healing applications, and the degradation and swelling properties of SA/PEO. The challenges and future directions of SA/PEO in the medical field are also discussed.

Keywords: sodium alginate, poly(ethylene oxide), electrospinning, wound healing

INTRODUCTION

Sodium alginate (SA) is a natural-based polymer derived from brown algae.[1] It has several attractive properties, such as non-toxicity, relatively low cost, hydrophilicity, biodegradability, and biocompatibility.[2] Sodium alginate also absorbs more water than its weight and binds metal ions that can cause oxidation to the skin, thereby providing beneficial skincare effects.[3,4]

In general, natural polymers are favoured over synthetic polymers in biomedical applications due to their biodegradation and biocompatibility; hence, natural polymers can be easily metabolised and cleared from the body.[5,6] However, some natural polymers have high viscosity due to their high molecular weight (Mw), while others are difficult to dissolve in suitable solvents or easily degraded in solutions. For such reasons, their mechanical properties and processing ability are often poor and it is usually more difficult to produce ultrafine fibres from natural polymers via electrospinning than synthetic polymers.[7-11] Therefore, the high viscosity and conductivity of the SA aqueous solution make it extremely difficult to fabricate nanofibrous structures using electrospinning.[12,13] To overcome this drawback, solution blends of natural and synthetic polymers have been prepared and spun into nanofibers.[14-17] Alginate nanofiber was obtained by combining it with poly(ethylene oxide) (PEO).[13] Poly(ethylene oxide) is a hydrophilic synthetic polymer that has been safely used in biomedical applications due to its non-toxicity, biocompatibility, and biodegradability properties.[18] Poly(ethylene oxide) has been used as a carrier for natural polymers (*e.g.*, alginate and chitosan) to facilitate

the electrospinning process.[19] Furthermore, the Food and Drug Administration (FDA) has also declared PEO as a safe material.[20]

To date, several methods have been developed to produce suitable polymeric nanofibers for wound dressings, including drawing, self-assembly, phase separation, template synthesis, and electrospinning.[21] Among these techniques, electrospinning is the most effective and useful technique for producing nanofibers from polymer solutions with controlled morphology.[22] The technique allows fibres to be fabricated with a high surface area because their diameters can be reduced to a few nanometres.[23] Electrospun fibre can be surface-functionalised to change the fibre surface's physical and chemical properties, whereas fibre morphology, spatial distribution, and structure can be controlled to achieve good mechanical properties, including the increase or decrease of tensile strength, modulus, and elongation.[24,25] In the development of biopolymers and fabrication methods, wound dressing materials should have exceptional properties that improve the wound healing process.[26] In the last decade, electrospun polymeric nanofibers have been used as wound dressings due to their ability to promote cell proliferation and bactericidal activity. Furthermore, the structural similarity with the extracellular matrix of normal skin gives an ideal support for cells and also their ability to deliver bioactive compounds to the wound site in a controllable manner.[27, 28] Consequently, wound dressings have been fabricated to cover wounds and improve the wound healing process.[29] A previous study fabricated a hybrid dressing that integrated the physical properties of the nanofiber structure and the therapeutic properties of the active compounds that are effective for wound healing.[28]

This review aims to focus on the electrospun SA/PEO nanofiber preparation for wound dressings. Therefore, the articles reviewed in this paper can assist researchers to gain a deeper understanding of the preparation of electrospun SA/PEO nanofiber with a view of using it in wound dressings. This review discusses and elaborates on the wound healing mechanism, currently available materials for wound dressings, and the use of SA/PEO as an alternative material for wound dressings. The basic concepts of electrospinning and the factors affecting the preparation and utilisation of SA/PEO blend nanofibers for wound dressing applications have also been discussed. Furthermore, the challenges and future prospects of SA/PEO blend nanofibers as wound dressings have been summarised.

WOUND HEALING MECHANISM

The entire wound healing process comprises four inter-related phases: haemostasis, inflammation, proliferation, and remodelling.[30,31] The first phase, haemostasis (Fig. 1a), is started by vascular constriction, induces blood coagulation and slows blood flow in the injured tissue area.[32] In this phase, injured vessels contract, reducing blood flow to the injured area and a fibrin clot is formed to prevent blood loss and avoid microbial contamination.[33] Platelets produce proteins, such as fibronectin, which cleaves into fibrin and creates a network, acting as an adhesive to bind platelets together, and fibrinogen, which causes exudates to coagulate. These proteins and others (*e.g.*, vitronectin, thrombospondin, platelets) form a clot that prevents future bleeding.[34,35]

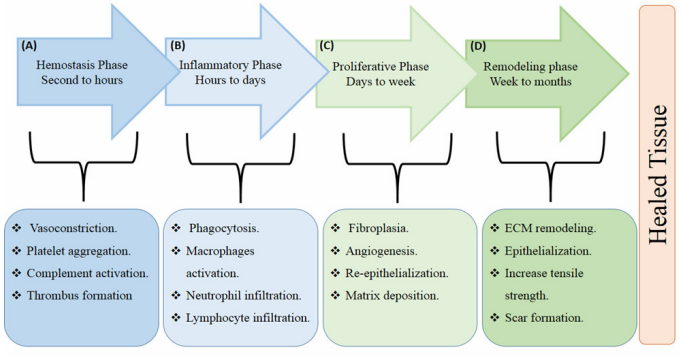

Figure 1: Wound healing phases (a) Hemostasis phase, (b) Inflammation phase, (c) Proliferation phase, (d) Remodeling phase

The inflammatory phase (Fig. 1b) begins almost simultaneously with haemostasis.[36] Platelets and mast cells in the injured tissue release chemical signals that cause blood vessels to dilate and capillary permeability to increase, allowing essential inflammatory cells like neutrophils, the 'first responders', to reach the injured area. Neutrophils produce factors necessary for the removal of bacteria and foreign objects.[34,35,37] In addition, monocytes differentiate into macrophages, which secrete multiple growth factors, cytokines, and remove apoptotic neutrophils and other cells. After 72 h, lymphocytes appear in the wound and exert a specific response against microbes (T-lymphocytes secrete cytokines involved in cytolytic activity, while B-lymphocytes produce antibodies).[33,38,39]

The inflammatory cells release TGF-β and PDGF that attract fibroblasts.[33] The proliferation stage (Fig. 1c) starts with the migration of fibroblasts to the wound site and the differentiation into myofibroblasts to produce extracellular matrix components.[33] Inflammatory cytokines promote re-epithelialisation as fibroblasts release growth factors, including epidermal growth factor, keratinocyte growth factor, and hepatocyte growth factor, which encourage keratinocytes to migrate towards the wound area and proliferate, forming a cover over the wound bed.[32,40]

The maturation stage (Fig. 1d), also known as remodelling, includes the replacement of granulation tissue by fibrous tissue, which is later modified to form a scar.[35,41] Macrophages, endothelial cells, and myofibroblasts leave the wound area, whereas the remaining undergoes apoptosis. The extracellular matrix (ECM) changes as well, with fibrillar collagen (type I) replacing reticular collagen (type III) produced in the proliferation stage. Meanwhile, the matrix metalloproteinases and lysyl enzyme produced by fibroblasts stimulate the reorientation of replaced collagen to increase the tensile strength of the newly formed tissue. Finally, the wound is healed by apoptosis and migration of the cells from the wound site, as well as extracellular matrix breakdown by matrix metalloproteinases.[42,43]

POTENTIAL OF BIOACTIVE AGENTS FOR WOUND HEALING

Traditional medicine is defined as the whole of the knowledge, practices, and skills based on the experiences of indigenous peoples, theories, and beliefs from various cultures that are used for health maintenance, as well as in the diagnosis, prevention, and treatment of diseases.[44] In the past, most medicinal products were obtained from plants, and today, a large number of drug products are extracted from plants, offering highly effective treatments for several diseases.[44] Herbal medicines include natural active compounds and nutrients that can be helpful in the treatment of wounds and other human diseases.[45] In general, natural metabolites from plants are the most common source of natural bioactive compounds, with various potential applications in the field of wound healing.[46]

Many natural bioactive metabolites (*e.g.*, tannins, flavonoids, alkaloids, saponins, terpenoids, phenols, essential oils, and fatty acids) have been investigated for potential application in wound healing.[46,47] For example, essential oils of lavender, thyme, rosemary, cinnamon, eucalyptus, tea tree, lemongrass, and peppermint have been shown to have antimicrobial activity and have been used as antibacterial agents in wound dressings.[48] Moreover, many herbal medicines have been used to improve wound healing.[49] Some of the herbal examples are *Orthosiphon aristatus* with antimicrobial, antioxidant, antidiabetic, and anti-inflammatory activities, and it is also responsible for wound contraction and increased epithelialisation rate due to the presence of flavonoids, phenolic acids, terpenoids, and phenolic compounds, such as rosmarinic acid, caffeic acid, eupatorin, and sinensetin.[50] *Centella asiatica* comprises natural bioactive compounds (*e.g.*, asiaticoside, asiatic acid, madecassoside, and madecassic acid) associated with the proliferation and production of collagen and protein at the wound area.[51] Green tea has antimicrobial, anti-inflammatory, and antioxidant properties due to the phenolic compounds present in the leaves known as catechins.[52] *Curcuma longa* root consists of curcumin, which stimulates granulation tissue growth, collagen deposition, and fibroblast proliferation in the healing of cutaneous wounds, as well as antioxidant, antibacterial, anti-inflammatory, and antifungal properties.[51] *Aloe vera* has many natural bioactive compounds that have been reported to have antibacterial, antioxidant, anti-inflammatory, antiviral, antifungal, antiseptic, and wound healing activities (*e.g.*, anthraquinones, saponins, glycosides, acemannan, oleic acid, pyrocatechol, phytol, and polysaccharides).[44,52]

TECHNIQUES FOR THE PREPARATION OF NANOFIBERS

Nanofibrous materials have attracted great interest in the last decade due to their various valuable uses in the biomedical and industrial fields. In order to satisfy the need for such materials, researchers have developed a variety of techniques to produce different types of nanostructured polymer dressings aimed at promoting wound healing and providing effective drug loading.[21] Several techniques are available for the preparation of nanofibers, including drawing, self-assembly, phase separation, template synthesis, and electrospinning.[21,53] The drawing technique is suitable for viscoelastic materials that can undergo strong deformation while possessing sufficient cohesion to hold up the developed stress by pulling and can be made into nanofibers during this process. The nanofibers are produced by touching a previously deposited polymer solution droplet with a sharp tip and drawing it as a liquid fibre, as shown in Figure 2a. However, this technique is limited to the laboratory scale, as nanofibers are produced one by one (*i.e.*, one fibre at a time), and heat-specific substrates and complex control equipment are required for the drawing phase, making its wide application impossible.[54] The self-assembly technique is a process in which small components organise to form nanofibers in a concentric manner by non-covalent forces, such as electrostatic reactions, hydrophobic forces, and hydrogen bonds. This process is difficult, lengthy, and highly elaborate with poor efficiency and lack of fine control of fibre dimensions.[55,56] The phase separation technique is very simple and consists of separate phases, involving dissolution of polymers, gelation, extraction using a different solvent, freezing, and freeze-drying under vacuum. The nanofibers are produced by dissolving the polymer in a solvent, keeping the solution at the gelation temperature, then removing the solvent and drying the matrix to form nanofibers, as shown in Figure 2b. The process is limited to the laboratory scale and is time-consuming, allowing to obtain only a small amount of nanofibers.[56] In the template synthesis technique, nanofibers can be prepared using a template-based synthesis. In this process, a nanostructured ceramic or polymeric membrane is used as the template and the targeting material is added in contact with the nanostructure to form nanofibers. Finally, the template is removed and nanofibers are obtained, as shown in Figure 2c. The template fabrication in this process is complex and the length of the fibre is limited to the template.[53]

The electrospinning technique is the most commonly technique for fabricating nanofibers and it has an advantage over the other techniques since it is the simplest and most inexpensive technique for producing fibres with desirable diameters.[53] The principles of this technique and the parameters will be discussed in more detail in the next section.

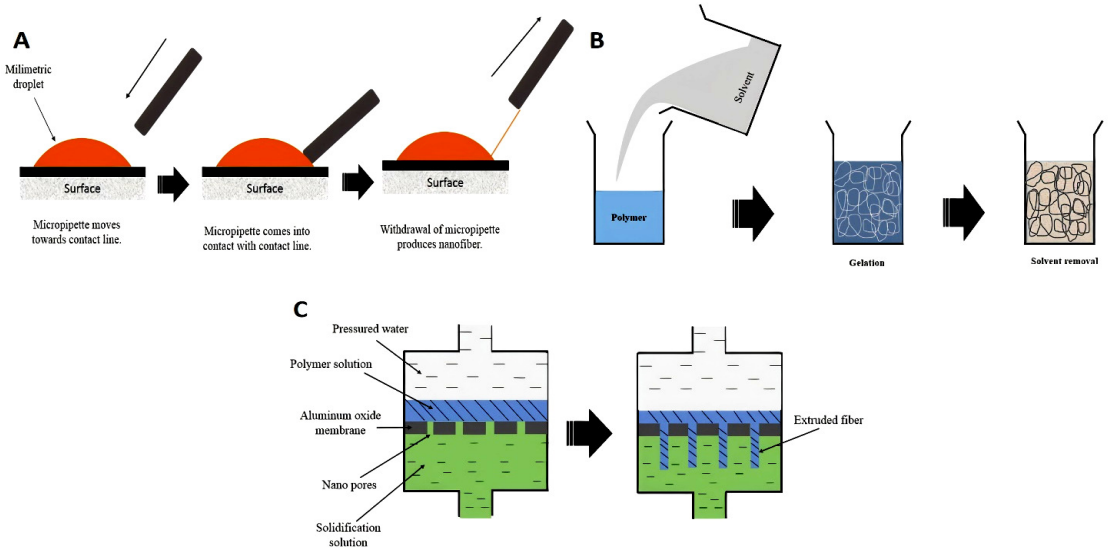

Figure 2: Techniques of nanofiber preparation, (A) drawing technique procedure, (B) phase separation technique, (C) template synthesis technique; adapted from Alghoraibi and Alomari[56]

Electrospinning technique

Principles of electrospinning

A basic electrospinning system (Fig. 3) consists of a high-voltage power supply, a syringe with a control pump, and a grounded collector.[57-60] In order to produce nanofibers, the collector is usually attached to the counter electrode and the polymer solution is pumped via the needle of the syringe.[61] The needle is then connected to the high-voltage electricity supply.[61] A Taylor cone is formed in the presence of an electric field as the polymer solution at the tip of the needle becomes electrostatically charged. If the electrostatic force overcomes the surface tension, the Taylor cone ejects a charged polymer solution.[22] The electric field accelerates the jet and becomes thinner when it moves into the grounded collector. If this occurs, the solvent evaporates rapidly, and the polymer chains within the jet begin to extend out and become oriented; subsequently, the jet solidifies into a nanofiber.[62-65]

Various nanofiber-based wound dressings prepared by the electrospinning method have been developed through time, and these can be classified as blend/simple electrospun nanofibers, core-shell nanofibers (emulsion and co-axial electrospun nanofibers), hybrid/multi-layer nanofibers, and drug conjugated nanofibers.[66]

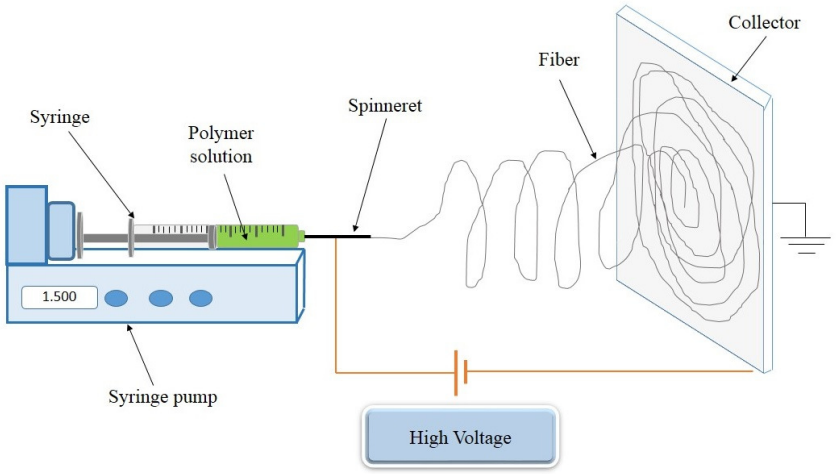

Figure 3: Electrospinning process (Bhardwaj and Kundu)[60]

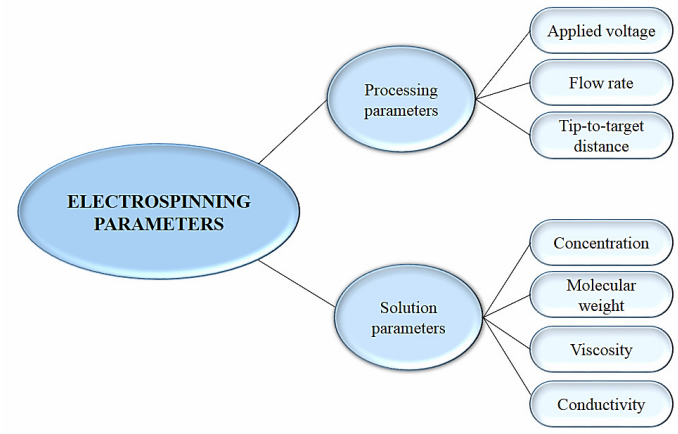

Figure 4: Schematic illustration of different parameters that affect the process of electrospinning

Electrospinning parameters

In order to produce nanofibers with improved performance in biomedical applications, the parameters involved in electrospinning should be studied with care.[22] These parameters include process parameters (voltage, tip-to-target distance, and flow rate) and solution parameters (concentration, molecular weight, viscosity, and conductivity), as shown in Figure 4.[22]

In general, most of the electrospinning parameters are interconnected and the optimum values differ from polymer to polymer.[59] The applied voltage is a crucial parameter to start the electrospinning process, and some studies have shown that a very high electrical field produced more beads and droplets.[67] However, in some cases, researchers have found that lower applied voltages could reduce the fibre diameter due to reduced flight speed, which may allow the jet to split.[68-70] The flow rate and the tip-to-target distance (*i.e*., the distance between the needle and the collector) will also have a significant impact on the morphology of fibre during electrospinning. An increase in the flow rate or a reduction in the tip-to-target gap will lead to a lack of time available for the solvent to evaporate, allowing the polymer strands to bind together, leading to bead formation.[22,58] In addition, a higher flow rate will provide more polymer solutions to replace those ejected as a fibre jet, resulting in an increase in fibre diameter.[67] For example, bead formation was observed for polystyrene fibre when the flow rate was increased to 0.10 mL/min. However, bead-free nanofibers were produced when the flow rate was reduced to 0.07 mL/min.[67,71] Besides, by reducing the tip-to-target distance, the fibre will stretch less because the jet has less time to stretch and orient, resulting in a larger fibre diameter.[22,71]

Viscosity is a critical parameter that determines a solution's spinnability.[72] Therefore, an optimum viscosity would usually lead to a less beaded and smoother fibre, with a small diameter and high mechanical strength.[59] However, if the viscosity becomes very low, the polymer molecules do not become entangled and beads or droplets are formed instead of fibres.[73] A further increase in viscosity can induce a hard ejection of the polymer solution through the tip of the needle.[35] The polymer's Mw affects different properties, such as viscosity, conductivity, surface tension, and polymer morphology. Low Mw polymers are likely to form beads rather than smooth fibres. Meanwhile, increased Mw allows the formation of smooth fibres.[35,74] The conductivity of the polymer solution can also have a major effect on fibre morphology. An increase in electrical conductivity reduces the diameter of the nanofibers. In contrast, a decrease in electrical conductivity produces beads, as the electrical forces are inadequate to allow the jet to elongate and produce uniform fibres.[60]

DRUG LOADING TECHNIQUES IN ELECTROSPUN NANOFIBERS

The electrospinning technique provides various options for drug incorporation. Drug molecules can be incorporated directly into the polymer fiber matrix or be attached to its surface.[75] Drug-loading techniques result in fibers with different drug-release kinetics and structures. Depending on the physicochemical properties of a drug, such as hydrophobicity, hydrophilicity, and molecular weight, various techniques can be used. The most suitable technique is also determined based on the type of drug to be loaded, such as proteins, genes, or small molecular drugs.[76] Several drug-loading techniques such as blending/simple, emulsion, coaxial and surface modification electrospinning have been used to incorporate medicinal compounds into electrospun fiber, as shown in Figure 5 and Table 1.[77]

Blend/simple electrospinning

In blend/simple electrospun nanofibers, polymers and bioactive molecules are dissolved in a suitable solvent. The consistency of solvents is a significant point in blend electrospinning. If the polymer and the bioactive agent can both be dissolved in the same solvent, the bioactive molecules are dissolved in the polymer solution directly. If more than one solvent is needed, the bioactive solution is prepared in a small quantity of another solvent before being added to the polymer solution.[73,78] The drug release is based on the homogeneity of the polymer solution with the bioactive substance, which is regulated either by diffusion/desorption or erosion/dissolution of the polymeric matrix.[79] It is important to understand the relationship between the hydrophilicity or hydrophobicity of bioactive molecules and polymer. The inability of bioactive molecules to dissolve in the polymer solution causes them to be deposited on the fiber surface, resulting in an undesirable explosive release of bioactive molecules.[80] This technique has been used by several researchers in biomedical applications.[81]

Co-axial and emulsion electrospinning (core-shell nanofibers)

The nanofibers with core-shell morphology can be obtained by using a co-axial needle or emulsion electrospinning.[66,79] Coaxial electrospinning is a modification of electrospinning in which a coaxial spinneret is used instead of a single spinneret to fabricate hybrid core-shell nanofibrous materials, bioactive agents embedded nanofibers, and nanotubes.[78]

The spinneret consists of two needles coaxially placed together (the core solution is pumped by the internal needle, while the shell solution is provided by the outer needle).[66] Emulsion electrospinning is a technique used to encapsulate bioactive molecules and protects them from deactivation or instability by avoiding direct contact with organic solvents.[78] It is classified into two types: water in oil (W/O) and oil in water (O/W). In W/O, the hydrophilic drugs are usually dissolved in the water phase and subsequently diffused into the oil phase, and vice versa in O/W. The surfactant/emulsifying agent is then added, and the mixture solution is vortexed to produce an emulsion.[76,79] The shell polymer in the case of W/O or O/W rapidly evaporates during electrospinning, causing the viscosity to increase. Therefore, the core solution droplets containing bioactive molecules migrate to the center of the jet as a result of the viscosity gradient.[82] After electrospinning, the W/O or O/W emulsion produces nanofibers with a core–shell structure, with the drugs in the core.[83, 84] The important condition is that the shell polymer should be an electrospinnable solution, whereas the core solution might be a non-spinnable liquid.[79] Therefore, the hydrophobic shell acts as an outer protective layer to prevent early burst release and can be used to control the release of drugs.[85] Core-shell nanofibers have been used to encapsulate macromolecules, such as DNA, as well as protection of the drug from the surrounding environment, which prevents drug degradation and controlling drug release.[86]

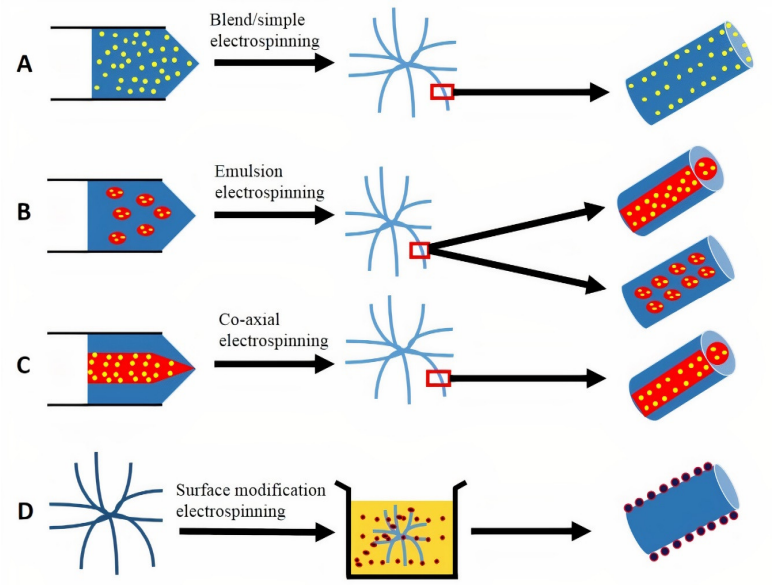

Figure 5: Drug loading techniques in electrospun nanofibers, (A) Blend/simple electrospinning, (B) Emulsion electrospinning, (C) Co-axial electrospinning, (D) Surface modification electrospinning (adapted from Wang and Windbergs)[75]

Surface modification electrospinning

Surface modification is the simple technique to attach the drug to the surface of fibers via chemical or physical interactions.[76] By physical interactions, the drug is attached on the surface through different forces, including electrostatic interactions, van der Waals forces, hydrophobic interactions and hydrogen bonding.[76,87] By chemical interactions, the drug is attached on the surface using hydroxy groups, carboxyl groups, thiols or amines. This technique was used to attach genes, proteins and antibiotics to nanofibrous scaffolds. Generally, a surface modified nanofiber mesh was used to prevent denaturation caused by organic solutions or solvents.[76,88]

Table 1
Different electrospinning techniques for drug loading of bioactive compounds

Polymer	Incorporation technique	Drug	Application	Condition	Results	Ref.
SA/PEO	Blend	Zinc oxide nanoparticles (ZnO-NPs)	Antibacterial wound dressing	*In vitro*	Alginate fibres embedded with ZnO-NPs have shown potential as novel, low-cost drug delivery systems.	158
SA/PEO	Blend	Vancomycin	Antibacterial wound dressing	*In vitro/ In vivo*	Nanofibers showed good antibacterial efficacy *in vitro* and *in vivo*.	159
SA/Poly(vinyl alcohol) (PVA)	Blend	Zinc oxide (ZnO)	Antibacterial wound dressing	*In vitro*	SA/PVA/ZnO mats showed antibacterial activity due to the presence of ZnO.	160
SA/PEO	Blend	Ciprofloxacin hydrochloride (CpHCl)	Drug delivery	*In vitro*	Uniform fibre with diameters of 119-161 nm was obtained and drug release was found to be of 24% in the first 20 h	129
SA/PVA	Blend	Honey	Wound dressing	*In vitro*	Honey/SA/PVA nanofibres could be a good choice for wound dressings.	161
PEO/poly(ε-caprolactone) (PCL)	Co-axial	Fibroblast growth factor 2 (FGF2)	Growth factor delivery for fibroblast proliferation	*In vitro*	PCL/PEO coaxial fibres containing FGF-2 significantly enhanced fibroblast cell viability and proliferation.	162
SA/PEO	Blend/Co-axial	Vitamin C (VC)	Drug delivery	*In vitro*	Core-shell nanofiber has the potential to be used for drug delivery due to its more controlled release of vitamin C.	124
Hyaluronic acid (HA)/PVA/PEO	Blend/Emulsion (O/W)	ZnO/cinnamon essential oil (CEO)	Wound dressing	*In vitro/ In vivo*	Metal nanoparticles and essential oil were incorporated with nanofibers to improve healing in a rat model.	163
SA/PEO	Blend/Emulsion (O/W)	Lavender oil	Wound dressing	*In vitro/ In vivo*	SA-PEO/LO nanofibres showed high antibacterial activity as well as the ability to reduce inflammation.	142
SA/PEO	Surface modification	Chitosan/silver nanoparticle (AgNPs) solution	Antibacterial wound dressings	*In vitro*	Chitosan/AgNPs were coated onto an electrospun alginate membrane to produce nanofiber composites with high antibacterial efficiency.	164

Additionally, it is appropriate for delivery of genes, enzymes, growth factors and macromolecules, such as heparin, which are difficult to dissolve homogeneously inside the polymer matrix via electrospinning.[77,89]

CURRENTLY AVAILABLE MATERIALS AS WOUND DRESSINGS

In the distant past, people used different materials, for instance, honey, linen, vegetable fibres, and animal fats as wound dressings to remove skin and pus to encourage wound healing.[26,90] However, these materials could not prevent bacterial infection and induce fast dehydration, as well as pain and bleeding when removed.[91] Currently, wound healing research has shown significant development in wound dressings by adding active ingredients, providing a moist environment, re-epithelialisation, collagen synthesis, and introducing angiogenesis to promote quick healing and infection control.[11,92] As mentioned before, an ideal wound dressing can prevent infection, restore skin structure and function, and accelerate healing.[23] Indeed, an ideal wound dressing is still far from the perfect criteria of wound healing. This drawback is due to the different characteristics of each wound and different stages of wound healing.[93]

Thus, several types of wound dressings have been developed, which can be classified into four main groups: passive, interactive, advanced, and bioactive wound dressings.[11] Passive wound dressing products, such as gauze, lint, plasters, natural bandages (cotton, wool, and cellulose), synthetic bandages (polyamide), and cotton wool are dry and do not control the amount of moisture in the wound bed.[11,93] They are inexpensive, available, and protect wounds from bacterial infiltration and mechanical trauma; however, as the dressing dries, it adheres to the wound and induces further injury and pain when removed.[29,92] Interactive dressings are polymeric films or foam dressings made of transparent silicones and polyurethanes.[26] These dressings, including hyaluronic acid hydrogels, and foam covers, are transparent and permeable to oxygen and water vapour, providing a temporary barrier against microbial penetration.[26] Nevertheless, these dressings with adhesive borders may damage surrounding tissues when removed.[92] These types of film dressings (*e.g.*, hydrogel dressings) can lead to foul smelling wounds in highly exudative wounds due to bacterial proliferation. Besides, foam dressings are not recommended for dry epithelialising wounds, dry scars, and low exuding wounds, as they depend on exudates for healing.[29,92,94,95]

Advanced dressings, such as hydrocolloids, alginates, and dressings fabricated by hydrodimers, can maintain wound environment moisture, thus facilitating healing.[11,96] Hydrocolloids are made up of pectin, elastomers, gelatine, and sodium carboxymethylcellulose materials; alginates are naturally composed of sodium salts of alginic acids; and hydrofibres are composed of soft non-woven sodium carboxymethylcellulose fibres.[11,94,97] In general, the attractive properties of these dressings are their biodegradability, preventing bacterial permeation, permeability to water vapour, and non-adhesiveness to wounds.[11] Some of them are used for highly exuding wounds as hydrofibres and alginate dressings, and also for dry wounds as hydrocolloid dressings.[11,29,98,99] However, hydrocolloid dressings are not recommended for neuropathic ulcers and are used on low to moderately exuding wounds, where large amounts of exudates can induce peri-wound maceration and off-floating of the dressing.[29] In addition, a secondary dressing is required for hydrofibres and alginate dressings to remain in place. Alginate dressings are also not recommended for dry wounds as they would adhere to the wound bed and cause pain sensation to the patient.[29,99,100]

The last type of wound dressing are bioactive dressings, which are composed of biopolymers (*e.g.*, collagen, hyaluronic acid, alginate, chitosan, and elastin).[29] These biopolymers can be used alone or in combination with other biopolymers based on the wound type and also combined with antimicrobials and growth factors.[29,92] This type of dressing was developed to allow interaction with the physiological condition of the wound in order to effectively enhance rapid healing of the wounds by facilitating proliferation and inflammation, decreasing scarring, and prolonging the use of the dressing.[11] Bioactive dressings have been reported to be good wound dressings, but are typically more expensive, depending on the drugs used.[29,99]

SODIUM ALGINATE AS AN ALTERNATIVE MATERIAL FOR WOUND DRESSINGS

Alginate is a common name for alginic acid salts that can be derived from the brown algae cell wall or synthesised by the metabolism of some bacteria.[101] It is a linear polysaccharide co-polymer that consists of two sterically different repeating units, (1→4)-a-L-guluronate (G unit) and (1→4)-b-D-mannuronate (M unit) in varying proportions, as shown in Figure 6a.[2,102] It is important to note that different sources of alginate provide a variety of chemical structures of polymers, such as alginate produced by *Azotobacter* bacteria, with a high concentration of G-blocks and its gel has relatively high stiffness.[103] Gelation of alginate results from interactions between Ca^{2+} ions and G residues, leading to chain-chain contact and junction zone formation, as shown in Figure 6b.[104,105] Selective binding of Ca^{2+} has been found to increase significantly with increased G residue content in the chains. In contrast, poly-M blocks and alternating MG blocks have lower selectivity towards the ion.[104] Furthermore, alginates containing monovalent cations (such as Na^+, NH_4^+, K^+) are soluble in cold and hot water and alginates containing divalent cations (such as Cu^{2+}, Zn^{2+}, Ni^{2+}) or trivalent cations (such as Ca^{2+}, Ba^{2+}, Sr^{2+}) are insoluble in water because they contain a terminal – COO- anion, so these cations link to it and produce an insoluble product.[106] Moreover, alginate will gradually form a gel when the pH value decreases (pH N<5) and is unaffected by the pH range of 5–11, while an increasing pH value (pH N >11) will reduce viscosity.[107] Commercial alginates have a molecular weight ranging from 32,000 to 400,000 g/mol, and while increasing the molecular weight of alginate can improve the physical properties of gels, higher viscosity is often undesirable in processing.[106] For example, proteins and cells may be damaged when mixed with a high viscosity alginate solution because of the high shear forces generated during mixing.[106]

Alginate-based nanofibers are potential materials for wound dressings. These nanofibers are similar to the extracellular matrix, thereby promoting the proliferation of epithelial cells and new tissue formation.[23,108,109] Moreover, their high effective surface area and small holes enhance haemostasis of injured tissues, promote fluid absorption, facilitate dermal drug delivery, enhance cell respiration, avoid bacterial infection, and provide high gas permeation.[23,108,109] In addition, alginate can also absorb up to 20 times its weight and can be used in moderately to severely exuding wounds.[110,111] To fabricate alginate nanofibers, researchers have used carrier polymers, such as poly(vinyl alcohol) (PVA) or poly(ethylene oxide) (PEO).[60] These carrier polymers are supposed to reduce the charge repulsions between the alginate chains, build hydrogen bonds, and improve the flexibility of the chain.[15,112,113]

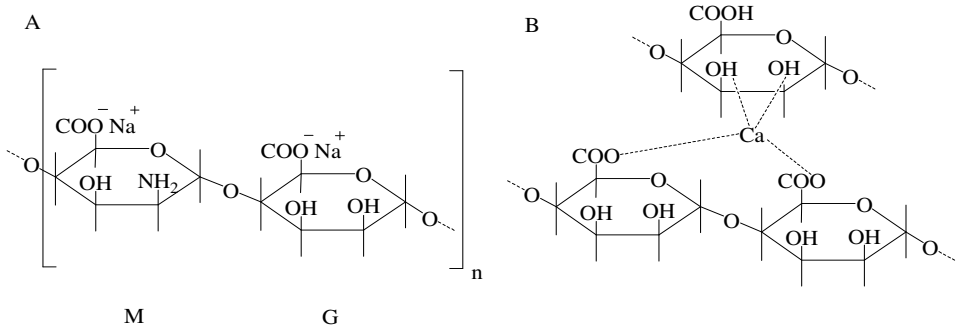

Figure 6: (A) Molecular structure of sodium alginate with (G) and (M) residues, and (B) structure of calcium alginate network describing crosslinking

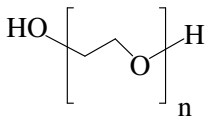

Figure 7: Molecular structure of PEO

POLY(ETHYLENE OXIDE) AS CO-POLYMER FOR NANOFIBER WOUND DRESSINGS

Poly(ethylene oxide) is a synthetic polymer prepared by the catalytic polymerisation of ethylene oxide, as shown in Figure 7.[114] The polymer can be produced using ethylene oxide with water, ethylene glycol, or ethylene glycol oligomers.[115,116] It can also be called polyethylene glycol (PEG), which is applied to a lower molar mass (< 100,000 g/mol), whereas higher Mw polymers (100,000 to 7 million g/mol) are classified as PEO.[114,117] It is a white, dry powder that is soluble in water and many organic solvents (*e.g*., chloroform, ethanol, methylene, and acetone).[114] The melting point of PEO ranges from 63 °C to 67 °C.[118] It can be dissolved in both cold and hot water, but when the solution temperature nears the boiling point of water, the polymers will precipitate out, which is known as the cloud point.[118]

For many years, PEO has been extensively used in biomedical, medical, and tissue engineering.[119-122] For example, different products have been developed using formulations with it, such as erodible and swellable implants and scaffolds for tissue engineering.[123] In addition, it is also used for skincare products and as a drug carrier in pharmaceutical industries.[124,125] In recent years, it has been used as a carrier polymer due to its advantages, such as good electrospinnability, suitability for biomedical applications, and also low cost.[126] Additionally, it has been commonly used for nanofiber synthesis due to water-soluble, non-toxic, and biodegradable properties.[5,127] In previous studies, it was used to enable electrospinning of natural polymers, for instance, chitosan, alginate, and silk fibroin, from which it is difficult to produce nanofibers on their own using electrospinning.[128-130] Therefore, it was selected as an acceptable candidate to be blended with alginate as it could improve the flexibility of alginate chains by modulating the repulsive forces between polyanions.[1,5] The oxygen of ether groups (R–O–R) in PEO can form a hydrogen bond with hydroxyl groups (-OH) on SA.[15]

SODIUM ALGINATE/POLY(ETHYLENE OXIDE) BLEND NANOFIBERS

Sodium alginate (SA) is a water-soluble polyelectrolyte. It is a challenge to create nanofibrous structures from SA using electrospinning owing to its high viscosity and conductivity.[2] These problems can be solved by blending SA with PEO, a non-toxic and biocompatible synthetic polymer, to reduce surface tension and viscosity, as shown in Table 2.[131,132] Moreover, a small amount of surfactant can be used to improve the electro-spinnability of the polymer solution and increase the alginate content in the solution.[131,132] Subsequent removal of PEO and surfactants can be achieved by soaking the nanofibers in water.[113]

A study by Park *et al*. reported that during electrospinning, fine alginate nanofibers with smooth and uniform fibres were obtained at the SA/PEO ratio of 1:2 and 2:2 (v/v). The combined cross-linking with calcium chloride ($CaCl_2$) improved the fibrous morphology and the uniform thickness of the smooth fibres at the SA/PEO ratio of 2:2 (v/v), compared to the SA/PEO ratio of 1:2 (v/v).[2] Another study by Safi *et al*. indicated that SA (2%, w/v)/PEO (8%, w/v), blended in the volume ratio of 50/50, could produce the finest uniform nanofibers with an average diameter of 99.1 nm. Also, the viscosity measurement of blended solutions found that an increase in PEO content reduced the viscosity of the alginate solution.[5] Meanwhile, a study by Hu *et al*. showed that smooth and homogeneous fibres with an average diameter of 105 nm were obtained with a total polymer concentration of 5% and the SA/PEO ratio of 1:1 (v/v).[101] Another study revealed that uniform fibres with a diameter of approximately 250 nm were obtained at a concentration of 3% and sodium SA/PEO ratio of 1:1–0:1 (v/v). A mixture of aqueous $CaCl_2$ and 2% hexamethylene diisocyanate (HMDI) cross-linking enhanced the water resistance of the electrospun fibres.[133] Saquing *et al*. reported that the alginate content of bead-free fibres increased up to 70 wt% with increased Mw of PEO by using 2 million g/mol of PEO and up to 85 wt% alginate content by adding the Triton X-100 surfactant.[131] However, defect-free fibres were not obtained at the lower Mw of PEO (100 and 200 kg/mol).[131] Hossain *et al*. demonstrated that the spinning solution of SA/PEO remained suitable for electrospinning during 10 days of storage time. After that, the viscosity of the spinning solution dropped over the next days, with 202 cP and 48 cP at 20 days and 40 days,

respectively. However, smooth and uniform nanofibers, with average diameters of 133 nm and 132 nm, were developed by solutions of 5 days and 10 days old, respectively. They also produced a stable electrospinning fibre jet, compared to the other solutions.[132]

Sa/PEO nanofibers loaded with drugs

Electrospun nanofibers with high porosity and large surface-to-volume ratio are a promising material in the drug delivery field, and are considered suitable dressing materials for wounds.[134,135] Therefore, a large number of polymers have been fabricated using electrospinning to be used as drug carriers due to their degradability and ability to encapsulate biomacromolecules and drugs.[77,136,137] Various studies have used SA and PEO for drug delivery due to the properties of SA (*e.g*., biocompatibility, low toxicity, biodegradability, and non-immunogenicity) and PEO (*e.g*., electrospinnability, hydrophilicity, and mechanical strength).[114,125,138] For example, according to Kyzioł *et al*. SA/PEO nanofibers loaded with ciprofloxacin hydrochloride (an antibiotic drug) were obtained by adding 2.0 wt% of PEO (1,000 kg/mol) and 1.0 wt% of Pluronic F-127. Furthermore, the nanofibers could even be loaded with 1.0 mg/mL of ciprofloxacin hydrochloride, without any adverse effect on the structure and morphology of the fibres.[129] Another study revealed that SA/PEO and soy protein isolated (SPI) blended fibres encapsulated with vancomycin (an antibiotic drug) were successfully electrospun to produce uniform fibres. The SA/PEO/SPI fibres provided a slower release of vancomycin in the initial stage, followed by a constant release compared to the SA/PEO fibres.[138] Dodero *et al*. reported that alginate-based nanofibers loaded with zinc oxide nanoparticles (ZnO-NPs) were highly porous and composed of good distribution of thin homogeneous nanofibers.[139] These properties show opportunities in tissue regeneration and drug delivery applications.[136,140] In addition, the rheological behaviour of SA/PEO solutions was affected by ZnO-NPs due to the ability of alginate molecules to develop electrostatic interaction and hydrogen bonds with ZnO-NPs.[139] Another study showed that electrospun nanofibers of SA/PEO loaded with curcumin (CU) were successfully developed for biomedical and filtering applications.[141]

Applications of drug-loaded Sa/PEO nanofibers in wound dressings

An ideal wound dressing is designed to promote the complete regeneration of the wounded tissue, successfully restore its biological activity and aesthetic appearance, while minimising inflammation and preventing microbial infection.[23,142] Drug-loaded nanofibers can be a suitable alternative to drug delivery systems to reduce the side effects caused by oral administration of drugs and provide quick action.[143] Drugs that are covalently bound to biodegradable polymers or scattered in a polymeric matrix can be control-released by the degradation of polymer.[125] Meanwhile, medicinal molecules with complex polymers can also be released from gels by diffusion.[125] Alginate-based dressings are desirable for their ability to maintain a moist environment around the wound, release bioactive compounds, and promote tissue re-epithelialisation.[26,39,142,144] A report by Hajiali et al. revealed that SA/PEO electrospun nanofibers loaded with essential lavender oil (LO) were successfully prepared via electrospinning. Furthermore, antibacterial and anti-inflammatory agents were released through diffusion from alginate-based nanofibers for more than 2 days. The SA/PEO/LO nanofibers reduced the risk of microbial infection by stopping the growth of Staphylococcus aureus.[142] Another study prepared electrospun nanofibers of SA/PEO loaded with acetaminophen (a painkiller drug). The nanofibers treated pain related to burn wounds efficiently, with fewer side effects than in the case of drugs administered by oral and intravenous routes. In the first 60 min, about 80% of the drug was released at pH 7.4 and only 56% of the drug was released at pH 5.5 up to 3 h. This reduced release is due to lower alginate swelling and solubility in acidic environments.[145] In another study by Abid et al., two layers of nanofibers were fabricated with different drugs via electrospinning. PEO nanofibers loaded with gabapentin (a strong nerve painkiller) were used as the contact layer for quick action, followed by SA nanofibers loaded with acetaminophen (a mild painkiller) as the second layer to synergise the effect. The combination of a strong nerve pain killer with a mild pain killer could be useful in reducing pain in burn patients, with fewer side effects.[143]

Table 2
Selected studies on spinnability of SA/PEO nanofibers

Name of polymers	Molecular weight of polymers (g/mol)		Concentration ratio of SA/PEO	Solvent	Drug	Surfactant	Optimal parameters				Results	Ref.
	SA	PEO					Voltage	Distance	Flow rate	Needle		
SA/PEO	-	9×10^5	1/2 and 2/2 wt%	D.W.	-	Lecithin (0.3 wt%)	0-40 kv	15 cm	0.2-1 mL/h	-	Uniform fibres	2
SA/PEO	-	6×10^5	3/9% (w/v) with volume ratio 30/70 and 50/50	D.W.	-	-	9 kV	12 cm	0.003 mL/m	-	Uniform fibres	102
SA/PEO	-	3×10^5	2/8% (w/v) with volume ratio of 50/50	D.W.	-	-	11 kV	10 cm	-	22 gauge needle	Uniform fibres	5
SA/PEO	1.96×10^5 / 3.7×10^4	6×10^5	2.4/1.6 wt% / 8.0/1.6 wt%	D.W.	-	Pluronic F127 (2 wt%)	10 - 15 kV	15 cm	0.50-0.75 mL/h	22 gauge needle	Uniform fibres	113
SA/PEO	1×10^5	2×10^6	3/3 wt% with volume ratio of 80/20	D.W.	-	Triton X-100 (1.5 wt%)	6–12 kV	15 cm	0.5 mL/h	-	Uniform fibres	131
SA/PEO	-	9×10^5	4/4 wt% with volume ratio of 70/30	D.W.	-	Triton X-100 (0.5 wt%)	12 kV	16 cm	0.3 mL/h	18 gauge needle	Uniform fibres	132
SA/PEO	-	1×10^6	3,4/2 wt%	D.W.	Cipro-floxacin	Pluronic F-127 (1.0 wt.%)	6-10 kV	15-20 cm	0.1-1.0 mL/h	22 gauge needle	Uniform fibres	129
SA/PEO	-	9×10^5	4/4 wt% with volume ratio of 80/20, 70/30	D.W.	-	Triton X-100 (0.5 wt%)	15 kV	20 cm	-	-	Uniform fibres	10
SA/PEO	$<4 \times 10^4$	1×10^6	8/4 wt% with volume ratio of 25/9.5	D.W.	Curcumin	Pluronic F-127 (2 wt %)	15-23 kV	15 cm	0.3-1 mL/h	-	Uniform fibres	141
SA/PEO	-	6×10^5	3/1.6 wt%	D.W.	-	Pluronic F-127 (1.5 wt %)	25 kV	-	0.2 mL/h	-	Uniform fibres	165
SA/PEO/SPI	1×10^5 – 2×10^5	1×10^6	3/3 wt% with volume ratio of 7/3	D.W.	Vanco-mycin	-	15 kV	15 cm	0.5 mL/h	22 gauge needle	Uniform fibres	138

It was observed that the drug was released in the first phase due to diffusion of the phosphate-buffered saline (PBS) solution into the free spaces of the fibre chains, whereas the release in the second phase might be due to the breaking of hydrogen bonding within the fibre chains. Additionally, the ionic cross-linking with calcium ions was used to avoid quick degradation of the fibre in the aqueous phase and, therefore, decreased the amount of drug released in the PBS environment.[129,143,146,147] In a study by S. Rezaei et al., PEO/SA nanofibers loaded with vitamin C (VC) were fabricated by two different electrospinning setups (core-shell and blended) for drug delivery. Based on the results of the drug release test, the release rate of core-shell nanofibers was lower than that of blended nanofibers due to the presence of VC further from the nanofiber surface.[124]

Degradation and swelling properties of Sa/PEO

In wound healing, the biodegradability of polymers is necessary during the wound healing stages for reducing the frequency of dressing changes, thus being less stressful and providing more comfort to the patient, as well as encouraging healing and increasing the cell growth rate due to their high compatibility with tissues and blood.[148] The degradation of natural and synthetic polymers requires cleavage of bonds responsive to enzymatic or hydrolytic activity. The rate of degradation is affected by the application site, the concentration and accessibility of enzymes, the chemical modifications made to their structure, and the proteolytic degradation caused by cells.[149] Furthermore, alginate-based nanofibers are ionically cross-linked in a calcium solution to convert SA into water-insoluble calcium alginate.[113,150] Calcium alginate is insoluble in water, slightly soluble in ethanol, but soluble in aqueous solutions, such as sodium carbonate, sodium phosphate, and substances capable of interacting with calcium ions. This property is essential for the application of haemostatic dressings and wound dressings.[151]

The crosslinking process enhances the degradation resistance of alginate nanofibers to support cell proliferation, while degrading over time to increase space for cell growth.[152] A study by Rezaei *et al*. reported that the degradation rate of SA/PEO nanofibers containing vitamin C was increased, which might be due to the presence of the –OH functional group of sodium alginate and the ability to ionize.[124] Slower degradation was also observed for crosslinker-treated samples, and it could be adjusted by changing the duration of the crosslinker treatment. For instance, increasing the duration of the crosslinker treatment increased the degradation time of the electrospun samples with high stability.[153] Another study used trifluoroacetic acid as a strong biocompatible crosslinking agent to improve the resistance of SA to water or aqueous body fluids.[141] SA/PEO nanofibers were prepared using two different molecular weights of alginate (*i.e*., lower Mw (37 kg/mol) and higher Mw (196 kg/mol) to study the effect of Mw on ionically crosslinked alginate degradation.[113] The lower Mw of alginates is convenient for *in vivo* tissue scaffolds, where they can be degraded and cleared from the body, whereas the higher Mw of alginates is ideal for topical use as a wound dressing due to its good mechanical properties.[113] Furthermore, membrane swelling is affected by the amount of PEO and crosslinker.[125] The swelling ratio increases when the amount of PEO increases, which may be due to the enhancement of hydrophilic polymer chains by the increase of PEO concentration.[125] On the other hand, the swelling ratio decreases when the amount of crosslinker increases, where polymeric chains may become rigid due to the contraction of microvoids (a microscopic void).[125] The swelling ratio is associated with drug release, where the increase of swelling ratio can increase drug release and *vice versa*.[143,154]

CHALLENGES AND FUTURE USE OF SA/PEO

As mentioned above, there are many challenges to prepare pure SA and SA/PEO nanofibers via electrospinning. Therefore, continuous and uniform nanofibrous structures from pure alginate solutions are difficult to obtain using this process. Many factors influence this issue, such as high gelation at low concentrations, rigid intermolecular and intramolecular hydrogen network, and their polyelectrolytic nature.[155] In order to solve this issue, SA has been blended with co-polymers, such as PEO, to facilitate its electrospinnability. However, there are other challenges when electrospinning SA/PEO to

obtain uniform nanofibrous structures, such as solution parameters (molecular weight, electrical conductivity, viscosity, and surface tension of polymers). Besides, the processing parameters (*e.g*., the voltage applied during electrospinning, the flow rate, and the distance from the tip to the collector) also affect the electrospinning process. From the work presented in this review, the ideal uniform nanofibrous structures have been achieved by controlling these parameters. SA/PEO nanofibers are easily dissolved in aqueous solutions, thus losing their stability. Hence, crosslinking using calcium ions or glutaraldehyde has been used to produce stable alginate nanofibers.[126] The challenges for wound healing applications include unsuitability for dry wounds, the need for a secondary dressing to keep it in place, and the ability to dehydrate if not covered.[109]

Alginate-based nanofibers are currently used clinically in wound healing applications. A multilayer dressing that covers most stages of wound healing can be a good option for potential applications in modern wound dressings. In addition, the nanofibers are considered promising candidates as carriers for drug delivery to improve wound healing and tissue regeneration. Furthermore, herbal medicines and their derivatives currently account for more than half of all medications taken globally due to recent advances in traditional medicine.[50,156] According to the World Health Organization, over 80% of people use herbal medicines, and there are over 21,000 plants with different medicinal properties.[157] Thus, the development of alginate dressings containing herbal medicines will play a more effective role in wound management in the future.

CONCLUSION

This review article presents an overview of studies published on SA/PEO blended nanofiber for wound dressings using electrospinning. The preparation of SA/PEO nanofiber has been discussed, in addition to the influence of molecular weight and concentration of blended polymers on the fibre properties, as well as the effect of electrospinning parameters on fibre morphology. SA/PEO nanofibers showed irregular morphology at lower concentrations of PEO polymer, whereas higher concentrations of PEO polymer produced nanofibers with regular morphology and uniform fibres. Besides, the alginate ratio could be increased by up to 85% using a higher Mw of PEO and a small amount of surfactant. Additionally, the developed SA/PEO nanofiber-based layer can be applied either alone or in combination with other layers for desirable outcomes. Nevertheless, further studies are needed to evaluate and develop innovative approaches in the field of the SA/PEO nanofibers prepared for wound dressing purposes. For example, preparing SA/PEO nanofiber wound dressings with dynamic and intelligent drug release, as well as carrying out sequential and continuous release, and multi-functionality, remains to be solved.

ACKNOWLEDGMENT: The authors thank Universiti Teknologi Malaysia for the financial support under the Research University Grant (Q.J130000.3554.07G36).

REFERENCES

[1] B. Vigani, S. Rossi, G. Milanesi, M. C. Bonferoni, G. Sandri *et al*., *Nanomaterials*, **8**, 971 (2018), https://doi.org/10.3390/nano8120971

[2] S. A. Park, K. E. Park and W. Kim, *Macromol. Res*., **18**, 891 (2010), https://doi.org/10.1007/s13233-010-0909-y

[3] A. Ammala, *Int. J. Cosmetic Sci*., **35**, 113 (2013), https://doi.org/10.1111/ics.12017

[4] S. Y. Byeon, M. K. Cho, K. H. Shim, H. J. Kim, H. G. Song *et al*., *J. Microbiol. Biotechnol*., **27**, 1657 (2017), https://doi.org/10.4014/jmb.1701.01025

[5] S. Safi, M. Morshed, S. A. H. Ravandi and M. Ghiaci, *J. Appl. Polym. Sci*., **104**, 3245 (2007), https://doi.org/10.1002/app.25696

[6] R. Song, M. Murphy, C. Li, K. Ting, C. Soo *et al*., *Drug Des. Devel. Ther*., **12**, 3117 (2018), https://doi.org/10.2147/DDDT.S165440

[7] Z. M. Huang, Y. Z. Zhang, S. Ramakrishna and C. T. Lim, *Polymer*, **45**, 5361 (2004), https://doi.org/10.1016/j.polymer.2004.04.005

[8] Y. Zhang, H. Ouyang, C. T. Lim, S. Ramakrishna and Z. M. Huang, *J. Biomed. Mater. Res. B Appl. Biomater*., **72**, 156 (2005), https://doi.org/10.1002/jbm.b.30128

[9] X. Xu, L. Yang, X. Xu, X. Wang, X. Chen *et al*., *J. Control. Release*, **108**, 33 (2005), https://doi.org/10.1016/j.jconrel.2005.07.021

[10] N. Bhattarai, Z. Li, D. Edmondson and M. Zhang, *Adv. Mater*., **18**, 1463 (2006), https://onlinelibrary.wiley.com/doi/abs/10.1002/adma.200502537

[11] A. Memic, T. Abudula, H. S. Mohammed, K. Joshi Navare, T. Colombani *et al*., *ACS Appl. Biol.*

Mater., **2**, 952 (2019), https://doi.org/10.1021/acsabm.8b00637
[12] J. M. Deitzel, J. D. Kleinmeyer, J. K. Hirvonen and N. C. B. Tan, *Polymer*, **42**, 8163 (2001), https://doi.org/10.1016/S0032-3861(01)00336-6
[13] J. Gutierrez-Gonzalez, E. Garcia-Cela, N. Magan and S. S. Rahatekar, *Mater. Lett*., **270**, 127662 (2020), https://doi.org/10.1016/J.Matlet.2020.127662
[14] B. Ding, E. Kimura, T. Sato, S. Fujita and S. Shiratori, *Polymer*, **45**, 1895 (2004), https://doi.org/10.1016/j.polymer.2004.01.026
[15] T. Caykara, S. Demirci, M. S. Eroğlu and O. Güven, *Polymer*, **46**, 10750 (2005)
[16] K. Miura, N. Kimura, H. Suzuki, Y. Miyashita and Y. Nishio, *Carbohyd. Polym*., **39**, 139 (1999), https://doi.org/10.1016/S0144-8617(98)00162-3
[17] P. Saini, M. Arora and M. Kumar, *Adv. Drug Deliv. Rev*., **107**, 47 (2016), https://doi.org/10.1016/j.addr.2016.06.014
[18] I. Solaberrieta, A. Jimenez, I. Cacciotti and M. C. Garrigos, *Polymers*, **12**, 1323 (2020), https://doi.org/10.3390/polym12061323
[19] M. Polaskova, P. Peer, R. Cermak and P. Ponizil, *Polymers*, **11**, 1384 (2019), https://doi.org/10.3390/polym11091384
[20] Y. L. Zhu, H. Y. Cui, C. Z. Li and L. Lin, *Food Packag. Shelf Life*, **21**, 100329 (2019), https://doi.org/10.1016/J.Fpsl.2019.100329
[21] A. M. Croitoru, D. Ficai, A. Ficai, N. Mihailescu, E. Andronescu *et al*., *Materials*, **13**, 2407 (2020), https://doi.org/10.3390/ma13102407
[22] G. Liu, Z. Gu, Y. Hong, L. Cheng and C. Li, *J. Control. Release*, **252**, 95 (2017), https://doi.org/10.1016/j.jconrel.2017.03.016
[23] M. Abrigo, S. L. McArthur and P. Kingshott, *Macromol. Biosci*., **14**, 772 (2014), https://doi.org/10.1002/mabi.201300561
[24] T. Lin, in "Book Nanofibers: Production, Properties and Functional Applications", edited by L. A. Tongs, BoD–Books on Demand, 2011
[25] R. Nayak, and R. Padhye, *J. Textile Eng. Fashion Technol*., **2**, 486 (2017), https://doi.org/10.15406/jteft.2017.02.00074
[26] P. Zahedi, I. Rezaeian, S. O. Ranaei-Siadat, S. H. Jafari and P. Supaphol, *Polym. Adv. Technol*., **21**, 77 (2010), https://doi.org/10.1002/pat.1625
[27] S. P. Miguel, D. R. Figueira, D. Simoes, M. P. Ribeiro, P. Coutinho *et al*., *Colloid. Surf. B*, **169**, 60 (2018), https://doi.org/10.1016/j.colsurfb.2018.05.011
[28] H. P. Felgueiras and M. T. P. Amorim, *Colloid. Surf. B*, **156**, 133 (2017), https://doi.org/10.1016/j.colsurfb.2017.05.001
[29] L. J. Borda, F. E. Macquhae and R. S. Kirsner, *Curr. Dermatol. Rep*., **5**, 287 (2016), https://doi.org/10.1007/s13671-016-0162-5
[30] P. Martin and R. Nunan, *Br. J. Dermatol*., **173**, 370 (2015), https://doi.org/10.1111/bjd.13954
[31] N. K. Rajendran, S. S. D. Kumar, N. N. Houreld and H. Abrahamse, *J. Drug Deliv. Sci. Technol*., **44**, 421 (2018), https://doi.org/10.1016/j.jddst.2018.01.009
[32] R. S. Ambekar and B. Kandasubramanian, *Eur. Polym. J*., **117**, 304 (2019), https://doi.org/10.1016/j.eurpolymj.2019.05.020
[33] F. M. Thiruvoth, D. P. Mohapatra, D. K. Sivakumar, R. Chittoria and V. Nandhagopal, *Plastic Aesthetic Res*., **2**, 250 (2015), https://doi.org/10.4103/2347-9264.158851
[34] J. Thomas, *Pract. Diabetes Int*. **22**, 283 (2005), https://doi.org/10.1002/pdi.848
[35] A. J. Hassiba, M. E. El Zowalaty, G. K. Nasrallah, T. J. Webster, A. S. Luyt *et al*., *Nanomedicine*, **11**, 715 (2016), https://doi.org/10.2217/nnm.15.211
[36] D. Simoes, S. P. Miguel, M. P. Ribeiro, P. Coutinho, A. G. Mendonca *et al*., *Eur. J. Pharm. Biopharm*., **127**, 130 (2018), https://doi.org/10.1016/j.ejpb.2018.02.022
[37] T. A. Wilgus, *Pharmacol. Res*., **58**, 112 (2008), https://doi.org/10.1016/j.phrs.2008.07.009
[38] P. Agrawal, S. Soni, G. Mittal and A. Bhatnagar, *Int. J. Low. Extrem. Wounds*, **13**, 180 (2014), https://doi.org/10.1177/1534734614544523
[39] L. I. Moura, A. M. Dias, E. Carvalho and H. C. de Sousa, *Acta Biomater*., **9**, 7093 (2013), https://doi.org/10.1016/j.actbio.2013.03.033
[40] G. F. Pierce, T. A. Mustoe, B. W. Altrock, T. F. Deuel and A. Thomason, *J. Cell. Biochem*., **45**, 319 (1991), https://doi.org/10.1002/jcb.240450403
[41] C. L. Baum and C. J. Arpey, *Dermatol. Surg*., **31**, 674 (2005), https://doi.org/10.1111/j.1524-4725.2005.31612
[42] V. L. Martins, M. Caley and E. A. O'Toole, *Cell Tissue Res*., **351**, 255 (2013), https://doi.org/10.1007/s00441-012-1410-z
[43] M. P. Caley, V. L. Martins and E. A. O'Toole, *Adv. Wound Care (New Rochelle)*, **4**, 225 (2015), https://doi.org/10.1089/wound.2014.0581
[44] M. M. Dan, P. Sarmah, D. R. Vana and A. Dattatreya, *Int. J. Med. Health Sci*., **7**, 170 (2018), https://www.indianjournals.com/ijor.aspx?target=ijor:ijmrhs&volume=7&issue=1&article=025
[45] S. Singh, R. Jangde and S. Daharwal, *Res. J. Pharm. Technol*., **12**, 3089 (2019), https://doi.org/10.5958/0974-360X.2019.00523.7
[46] A. Moeini, P. Pedram, P. Makvandi, M. Malinconico and G. G. d'Ayala, *Carbohyd. Polym*., **233**, 115839 (2020), https://doi.org/10.1016/j.carbpol.2020.115839
[47] R. Bahramsoltani, M. H. Farzaei and R. Rahimi, *Arch. Dermatol. Res*., **306**, 601 (2014), https://doi.org/10.1007/s00403-014-1474-6
[48] I. Negut, V. Grumezescu and A. M. Grumezescu, *Molecules*, **23**, 2392 (2018), https://doi.org/10.3390/molecules23092392
[49] R. Varghese and V. Shinde, *Int. J. Pharmacogn*., **8**, 14 (2021),

https://doi.org/10.13040/IJPSR.0975-8232.IJP.8(1).14-24
[50] F. I. Abdullah, L. S. Chua, S. P. M. Bohari and E. Sari, *Nat. Prod. Commun.*, **15**, 1934578X20953308 (2020), https://doi.org/10.1177/1934578X20953308
[51] A. Sharma, S. Khanna, G. Kaur and I. Singh, *Future J. Pharm. Sci.*, **7**, 1 (2021), https://doi.org/10.1186/s43094-021-00202-w
[52] P. Fatehi, and M. Abbasi, *J. Tissue Eng. Regen. Med.*, **14**, 1527 (2020), https://doi.org/10.1002/term.3119
[53] J. Sharma, M. Lizu, M. Stewart, K. Zygula, Y. Lu *et al.*, *Polymers*, **7**, 186 (2015), https://doi.org/10.3390/polym7020186
[54] A. A. Almetwally, M. El-Sakhawy, M. Elshakankery and M. Kasem, *J. Text. Assoc.*, **78**, 5 (2017)
[55] X. W. Zhang, and Y. Lu, *Polym. Rev.*, **54**, 677 (2014), https://doi.org/10.1080/15583724.2014.935858
[56] I. Alghoraibi and S. Alomari, in "Handbook of Nanofibers", edited by A. Barhoums, 2018, p. 1-46, https://doi.org/10.1007/978-3-319-42789-8_11-2
[57] D. Li and Y. Xia, *Adv. Mater.*, **16**, 1151 (2004), https://doi.org/10.1002/adma.200400719
[58] T. J. Sill and H. A. von Recum, *Biomaterials*, **29**, 1989 (2008), https://doi.org/10.1016/j.biomaterials.2008.01.011
[59] A. Balaji, M. V. Vellayappan, A. A. John, A. P. Subramanian, S. K. Jaganathan *et al.*, *RSC Adv.*, **5**, 57984 (2015), https://doi.org/10.1039/c5ra07595e
[60] N. Bhardwaj and S. C. Kundu, *Biotechnol. Adv.*, **28**, 325 (2010), https://doi.org/10.1016/j.biotechadv.2010.01.004
[61] R. S. Bhattarai, R. D. Bachu, S. H. S. Boddu and S. Bhaduri, *Pharmaceutics*, **11**, 5 (2019), https://doi.org/10.3390/pharmaceutics11010005
[62] A. Rezaei, A. Nasirpour and M. Fathi, *Compr. Rev. Food Sci. Food Saf.*, **14**, 269 (2015), https://doi.org/10.1111/1541-4337.12128
[63] H. F. Liu, X. L. Ding, G. Zhou, P. Li, X. Wei *et al.*, *J. Nanomater.*, **2013**, (2013), https://doi.org/10.1155/2013/495708
[64] S. Qi and D. Craig, *Adv. Drug Deliv. Rev.*, **100**, 67 (2016), https://doi.org/10.1016/j.addr.2016.01.003
[65] C. Kriegel, A. Arecchi, K. Kit, D. J. McClements and J. Weiss, *Crit. Rev. Food Sci. Nutr.*, **48**, 775 (2008), https://doi.org/10.1080/10408390802241325
[66] D. Madhukiran, A. Jha, M. Kumar, G. Ajmal, G. V. Bonde *et al.*, *Expert. Opin. Drug Deliv.*, **18**, 25 (2021), https://doi.org/10.1080/17425247.2021.1823966
[67] A. Haider, S. Haider and I. K. Kang, *Arab. J. Chem.*, **11**, 1165 (2018), https://doi.org/10.1016/j.arabjc.2015.11.015
[68] C. S. Ki, D. H. Baek, K. D. Gang, K. H. Lee, I. C. Um *et al.*, *Polymer*, **46**, 5094 (2005), https://doi.org/10.1016/j.polymer.2005.04.040
[69] H. Jiang, P. Zhao and K. Zhu, *Macromol. Res.*, **7**, 517 (2007), https://doi.org/10.1002/mabi.200600277
[70] C. Yao, X. Li and T. Song, *J. Appl. Polym. Sci.*, **103**, 380 (2007), https://doi.org/10.1002/app.24619
[71] S. Megelski, J. S. Stephens, D. B. Chase and J. F. Rabolt, *Macromolecules*, **35**, 8456 (2002)
[72] S. Jiang, L. P. Lv, K. Landfester and D. Crespy, *Acc. Chem. Res.*, **49**, 816 (2016), https://doi.org/10.1021/acs.accounts.5b00524
[73] V. Pillay, C. Dott, Y. E. Choonara, C. Tyagi, L. Tomar *et al.*, *J. Nanomater.*, **2013**, (2013), https://doi.org/10.1155/2013/789289
[74] E. P. Tan, S. Y. Ng and C. T. Lim, *Biomaterials*, **26**, 1453 (2005), https://doi.org/10.1016/j.biomaterials.2004.05.021
[75] J. Wang and M. Windbergs, *Eur. J. Pharm. Biopharm.*, **119**, 283 (2017), https://doi.org/10.1016/j.ejpb.2017.07.001
[76] R. Jain, S. Shetty and K. S. Yadav, *J. Drug Deliv. Sci. Technol.*, **57**, 101604 (2020), https://doi.org/10.1016/j.jddst.2020.101604
[77] Q. Zhang, Y. C. Li, Z. Y. Lin, K. K. Y. Wong, M. Lin *et al.*, *Drug Discov. Today*, **22**, 1351 (2017), https://doi.org/10.1016/j.drudis.2017.05.007
[78] S. Fahimirad and F. Ajalloueian, *Int. J. Pharm.*, **566**, 307 (2019), https://doi.org/10.1016/j.ijpharm.2019.05.053
[79] M. Buzgo, A. Mickova, M. Rampichova and M. Doupnik, in "Core-Shell Nanostructures for Drug Delivery and Theranostics", edited by L. Overend, M. L. Focarete and A. Tampieris, Elsevier, 2018, p. 325-347, https://doi.org/10.1016/B978-0-08-102198-9.00011-9
[80] A. T. Iacob, M. Dragan, O. M. Ionescu, L. Profire, A. Ficai *et al.*, *Pharmaceutics*, **12**, 983 (2020), https://doi.org/10.3390/pharmaceutics12100983
[81] Y. Sun, S. H. Cheng, W. J. Lu, Y. F. Wang, P. P. Zhang *et al.*, *RSC Adv.*, **9**, 25712 (2019), https://doi.org/10.1039/c9ra05012d
[82] N. Nikmaram, S. Roohinejad, S. Hashemi, M. Koubaa, F. J. Barba *et al.*, *RSC Adv.*, **7**, 28951 (2017), https://doi.org/10.1039/c7ra00179g
[83] P. Coimbra, J. P. Freitas, T. Goncalves, M. H. Gil and M. Figueiredo, *Mater. Sci. Eng. C*, *Mater. Biol. Appl.*, **94**, 86 (2019), https://doi.org/10.1016/j.msec.2018.09.019
[84] X. Liu, H. Xu, M. Zhang and D. G. Yu, *Membranes*, **11**, 770 (2021), https://doi.org/10.3390/membranes11100770
[85] B. Pant, M. Park and S. J. Park. *Pharmaceutics*, **11**, 305 (2019), https://doi.org/10.3390/pharmaceutics11070305
[86] M. Rahmani, S. A. Bidgoli and S. M. Rezayat, *Nanomed. J.*, **4**, 61 (2017), https://doi.org/10.22038/nmj.2017.21210.1224

[87] A. J. Meinel, O. Germershaus, T. Luhmann, H. P. Merkle and L. Meinel, *Eur. J. Pharm. Biopharm.*, **81**, 1 (2012), https://doi.org/10.1016/j.ejpb.2012.01.016
[88] F. Zhou, X. Jia, Y. Yang, Q. Yang, C. Gao *et al.*, *Acta Biomater.*, **43**, 303 (2016), https://doi.org/10.1016/j.actbio.2016.07.048
[89] X. Qiu, B. L. Lee, X. Ning, N. Murthy, N. Dong *et al.*, *Acta Biomater.*, **51**, 138 (2017), https://doi.org/10.1016/j.actbio.2017.01.012
[90] G. Broughton, J. E. Janis and C. E. Attinger, *Plast. Reconstr. Surg.*, **117**, 6S (2006), https://doi.org/10.1097/01.prs.0000225429.76355.dd
[91] B.-M. Neamtu and A. Barbu, *Acta Medica Transilvanica*, **24**, 84 (2019), http://www.amtsibiu.ro/Arhiva/2019/Nr3-en/Neamtu.pdf
[92] S. Dhivya, V. V. Padma and E. Santhini, *BioMedicine*, **5**, (2015), https://doi.org/10.7603/s40681-015-0022-9
[93] K. A. Krishnan and S. Thomas, *Polym. Adv. Technol.*, **30**, 823 (2019), https://doi.org/10.1002/pat.4540
[94] C. Weller and G. Sussman, *J. Pharm. Pract. Res.*, **36**, 318 (2006), https://doi.org/10.1002/j.2055-2335.2006.tb00640.x
[95] J. G. Powers, L. M. Morton and T. J. Phillips, *Dermatol. Ther.*, **26**, 197 (2013), https://doi.org/10.1111/dth.12055
[96] L. Wei, *Open Med.*, **10**, 452 (2015), https://doi.org/10.1515/med-2015-0078
[97] Y. Barnea, J. Weiss and E. Gur, *Ther. Clin. Risk Manag.*, **6**, 21 (2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2817785/
[98] N. F. Watson and W. Hodgkin, *Surgery (Oxford)*, **23**, 52 (2005), https://doi.org/10.1383/surg.23.2.52.60345
[99] J. S. Boateng, K. H. Matthews, H. N. Stevens and G. M. Eccleston, *J. Pharm. Sci.*, **97**, 2892 (2008), https://doi.org/10.1002/jps.21210
[100] C. Wiegand, J. Tittelbach, U.-C. Hipler and P. Elsner, *Chronic Wound Care Manag. Res.* **2**, 101 (2015), https://doi.org/10.2147/CWCMR.S60315
[101] C. Hu, R. H. Gong and F. L. Zhou, *Int. J. Polym. Sci.*, **2015**, (2015), https://doi.org/10.1155/2015/126041
[102] S. Moon, B. Y. Ryu, J. Choi, B. Jo and R. J. Farris, *Polym. Eng. Sci.*, **49**, 52 (2009), https://doi.org/10.1002/pen.21216
[103] I. D. Hay, Z. U. Rehman, A. Ghafoor and B. H. A. Rehm, *J. Chem. Technol. Biotechnol.*, **85**, 752 (2010), https://doi.org/10.1002/jctb.2372
[104] H. Hecht and S. Srebnik, *Biomacromolecules*, **17**, 2160 (2016), https://doi.org/10.1021/acs.biomac.6b00378
[105] S. Djomehri, "Diffusive and Mechanical Properties of biodegradable Alginate Stents", San Jose State University, 2013
[106] I. I. Kabir, C. C. Sorrell, S. S. Mofarah, W. Yang, A. C. Y. Yuen *et al.*, *Polym. Rev.*, **61**, 357 (2021), https://doi.org/10.1080/15583724.2020.1801726
[107] X. Guo, Y. Wang, Y. Qin, P. Shen and Q. Peng, *Int. J. Biol. Macromol.*, **162**, 618 (2020), https://doi.org/10.1016/j.ijbiomac.2020.06.180
[108] Y. Zhang, C. T. Lim, S. Ramakrishna and Z. M. Huang, *J. Mater. Sci. Mater. Med.*, **16**, 933 (2005), https://doi.org/10.1007/s10856-005-4428-x
[109] B. A. Aderibigbe and B. Buyana, *Pharmaceutics*, **10**, 42 (2018), https://doi.org/10.3390/pharmaceutics10020042
[110] S. O'Meara and M. Martyn-St James, *Cochrane Database Syst. Rev.*, CD010182 (2013), https://doi.org/10.1002/14651858.CD010182.pub2
[111] C. D. Weller, V. Team and G. Sussman, *Front. Pharmacol.*, **11**, 155 (2020), https://doi.org/10.3389/fphar.2020.00155
[112] H. Nie, A. He, J. Zheng, S. Xu, J. Li *et al.*, *Biomacromolecules*, **9**, 1362 (2008), https://doi.org/10.1021/bm701349j
[113] C. A. Bonino, M. D. Krebs, C. D. Saquing, S. I. Jeong, K. L. Shearer *et al.*, *Carbohyd. Polym.*, **85**, 111 (2011), https://doi.org/10.1016/j.carbpol.2011.02.002
[114] M. P. Riya, K. A. Antu, T. Vinu, K. C. Chandrakanth, K. S. Anilkumar *et al.*, *J. Sci. Food Agric.*, **94**, 943 (2014), https://doi.org/10.1002/jsfa.6340
[115] J. Kahovec, R. B. Fox and K. Hatada, *Pure Appl. Chem.*, **74**, 1921 (2002), https://doi.org/10.1351/pac200274101921
[116] J. W. Jung, and J. W. Hu, *Sustainability*, **9**, 62 (2017), https://doi.org/10.3390/Su9010062
[117] L. R. T. Coelho, Master's Thesis, Universidade Nova de Lisboa, 2018, https://run.unl.pt/handle/10362/57610
[118] L. Ma, L. Deng and J. Chen, *Drug Dev. Ind. Pharm.*, **40**, 845 (2014), https://doi.org/10.3109/03639045.2013.831438
[119] E. E. Brown and M.-P. G. Laborie, *Biomacromolecules*, **8**, 3074 (2007), https://doi.org/10.1021/bm700448x
[120] H. Kaczmarek, K. Bajer, P. Galka and B. Kotnowska, *Polym. Degrad. Stab.*, **92**, 2058 (2007), https://doi.org/10.1016/j.polymdegradstab.2007.07.019
[121] Z. Cai and J. Kim, *Cellulose*, **17**, 83 (2010), https://doi.org/10.1007/s10570-009-9362-5
[122] F. Safdari, P. J. Carreau, M. C. Heuzey, M. R. Kamal and M. M. Sain, *Cellulose*, **24**, 755 (2017), https://doi.org/10.1007/s10570-016-1137-1
[123] M. A. Rahman, M. A. Khan and S. M. Tareq, *J. Appl. Polym. Sci.*, **117**, 2075 (2010), https://doi.org/10.1002/app.32034
[124] S. Rezaei, A. Valipouri, S. A. Hosseini Ravandi, M. Kouhi and L. Ghasemi Mobarakeh, *Polym. Adv. Technol.*, **30**, 2447 (2019), https://doi.org/10.1002/pat.4692

[125] B. Mallikarjuna, K. M. Rao, S. Siraj, A. C. Babu, K. C. Rao *et al*., *Des. Monom. Polym*., **16**, 151 (2013), https://doi.org/10.1080/15685551.2012.705503
[126] M. A. Taemeh, A. Shiravandi, M. A. Korayem and H. Daemi, *Carbohyd. Polym*., **228**, 115419 (2020), https://doi.org/10.1016/j.carbpol.2019.115419
[127] D. Surendhiran, H. Y. Cui and L. Lin, *Food Packag. Shelf Life*, **21**, 100346 (2019), https://doi.org/10.1016/J.Fpsl.2019.100346
[128] T. T. Yuan, P. M. Jenkins, A. M. D. Foushee, A. R. Jockheck-Clark and J. M. Stahl, *J. Nanomater*., **2016**, (2016), https://doi.org/10.1155/2016/6231040
[129] A. Kyzioł, J. Michna, I. Moreno, E. Gamez and S. Irusta, *Eur. Polym. J*., **96**, 350 (2017), https://doi.org/10.1016/j.eurpolymj.2017.09.020
[130] S. Lin, M. Chen, H. Jiang, L. Fan, B. Sun *et al*., *Colloids Surf. B*, **139**, 156 (2016), https://doi.org/10.1016/j.colsurfb.2015.12.001
[131] C. D. Saquing, C. Tang, B. Monian, C. A. Bonino, J. L. Manasco *et al*., *Ind. Eng. Chem. Res*., **52**, 8692 (2013), https://pubs.acs.org/doi/abs/10.1021/ie302385b
[132] M. F. Hossain, M. Rahman and M. G. Nur, *Eur. Sci. J*., **13**, 56 (2017), https://doi.org/10.19044/esj.2017.v13n9p56
[133] J. W. Lu, Y. L. Zhu, Z. X. Guo, P. Hu and J. Yu, *Polymer*, **47**, 8026 (2006), https://doi.org/10.1016/j.polymer.2006.09.027
[134] H. Lee, G. Xu, D. Kharaghani, M. Nishino, K. H. Song *et al*., *Int. J. Pharm*. **531**, 101 (2017), https://doi.org/10.1016/j.ijpharm.2017.08.081
[135] D. G. Yu, X. X. Shen, C. Branford-White, K. White, L. M. Zhu *et al*., *Nanotechnology*, **20**, 055104 (2009), https://doi.org/10.1088/0957-4484/20/5/055104
[136] M. Zamani, M. P. Prabhakaran and S. Ramakrishna, *Int. J. Nanomedicine*, **8**, 2997 (2013), https://doi.org/10.2147/IJN.S43575
[137] J. Wu, Z. Zhang, J. Gu, W. Zhou, X. Liang *et al*., *J. Control. Release*, **320**, 337 (2020), https://doi.org/10.1016/j.jconrel.2020.01.020
[138] R. Wongkanya, P. Chuysinuan, C. Pengsuk, S. Techasakul, K. Lirdprapamongkol *et al*., *J. Sci. Adv. Mater. Dev*., **2**, 309 (2017), https://doi.org/10.1016/j.jsamd.2017.05.010
[139] A. Dodero, M. Alloisio, S. Vicini and M. Castellano, *Carbohyd. Polym*., **227**, 115371 (2020), https://doi.org/10.1016/j.carbpol.2019.115371
[140] K. Sasikanth, S. Nama, S. Suresh and B. Brahmaiah, *Pharma Innov*., **2**, 118 (2013)
[141] G. G. Javier, G.-C. Esther, N. Magan and S. S. Rahatekar, *Mater. Lett*., **270**, 127662 (2020), https://doi.org/10.1016/j.matlet.2020.127662
[142] H. Hajiali, M. Summa, D. Russo, A. Armirotti, V. Brunetti *et al*., *J. Mater. Chem. B*, **4**, 1686 (2016), https://doi.org/10.1039/C5TB02174J
[143] S. Abid, T. Hussain, A. Nazir, A. Zahir and N. Khenoussi, *Polym. Bull*., **76**, 6387 (2019), https://doi.org/10.1007/s00289-019-02727-w
[144] K. Y. Lee and D. J. Mooney, *Prog. Polym. Sci*., **37**, 106 (2012), https://doi.org/10.1016/j.progpolymsci.2011.06.003
[145] S. Abid, T. Hussain, A. Nazir, A. Zahir and N. Khenoussi, *Mater. Res. Express*., **5**, 085017 (2018), https://doi.org/10.1088/2053-1591/Aad2eb
[146] J. Siepmann and N. A. Peppas, *Adv. Drug Deliv. Rev*. **64**, 163 (2012), https://doi.org/10.1016/j.addr.2012.09.028
[147] D. Caccavo, S. Cascone, G. Lamberti and A. A. Barba, *Mol. Pharm*., **12**, 474 (2015), https://doi.org/10.1021/mp500563n
[148] B. Azimi, H. Maleki, L. Zavagna, J. G. De la Ossa, S. Linari et al., *J. Funct. Biomater*., **11**, 67 (2020), https://doi.org/10.3390/jfb11030067
[149] H. P. Felgueiras, T. Tavares and M. Amorim, in *Procs. IOP Conference Series*: *Materials Science and Engineering*, 2019, vol. 634, ID 012033
[150] S. P. Bohari, D. W. Hukins and L. M. Grover, *Biomed. Mater. Eng*., **21**, 159 (2011), https://doi.org/10.3233/BME-2011-0665
[151] A. L. Vega-Avila, O. Perales-Perez and R. V. Rullan, in "Electrospun Biomaterials and Related Technologies", Springer, 2017, p. 109-147, https://doi.org/10.1007/978-3-319-70049-6_4
[152] M. Norouzi, S. M. Boroujeni, N. Omidvarkordshouli and M. Soleimani, *Adv. Healthc. Mater*., **4**, 1114 (2015), https://doi.org/10.1002/adhm.201500001
[153] H. Hajiali, J. A. Heredia-Guerrero, I. Liakos, A. Athanassiou and E. Mele, *Biomacromolecules*, **16**, 936 (2015), https://doi.org/10.1021/bm501834m
[154] A. G. Sullad, L. S. Manjeshwar and T. M. Aminabhavi, *Ind. Eng. Chem. Res*., **49**, 7323 (2010), https://doi.org/10.1021/ie100389v
[155] T. C. Mokhena, M. J. Mochane, A. Mtibe, M. J. John, E. R. Sadiku et al., *Materials*, **13**, 934 (2020), https://doi.org/10.3390/Ma13040934
[156] A. Shedoeva, D. Leavesley, Z. Upton and C. Fan, *Evid. Based Compl. Altern. Med*., **2019** (2019), https://doi.org/10.1155/2019/2684108
[157] P. Nasa and H. Kumar, *J. Pharm. Sci. Res*., **12**, 1071 (2020)
[158] A. Dodero, S. Vicini, P. Lova, M. Alloisio and M. Castellano, *Int. J. Biol. Macromol*., **165**, 1939 (2020), https://doi.org/10.1016/j.ijbiomac.2020.10.116
[159] H. A. Fathi, A. Abdelkader, M. S. AbdelKarim, A. A. Abdelaziz, M. A. El-Mokhtar *et al*., *Int. J. Pharm*., **586**, 119620 (2020), https://doi.org/10.1016/j.ijpharm.2020.119620
[160] K. T. Shalumon, K. H. Anulekha, S. V. Nair, S. V. Nair, K. P. Chennazhi *et al*., *Int. J. Biol. Macromol*., **49**, 247 (2011), https://doi.org/10.1016/j.ijbiomac.2011.04.005
[161] Y. D. Tang, X. Z. Lan, C. F. Liang, Z. X. Zhong, R. T. Xie *et al*., *Carbohyd. Polym*., **219**,

113 (2019), https://doi.org/10.1016/j.carbpol.2019.05.004
[162] M. Rubert, J. Dehli, Y. F. Li, M. B. Taskin, R. Xu *et al*., *J*. *Mater*. *Chem*. *B*, **2**, 8538 (2014), https://doi.org/10.1039/c4tb01258e
[163] R. Mohamed, N. G. El-Beheri, M. M. Agwa, H. M. Eltaher, M. Alseqely *et al*., *Int*. *J*. *Biol*. *Macromol*., **167**, 1552 (2021), https://doi.org/10.1016/j.ijbiomac.2020.11.109
[164] T. C. Mokhena and A. S. Luyt, *Carbohyd*. *Polym*., **165**, 304 (2017), https://doi.org/10.1016/j.carbpol.2017.02.068
[165] T. K. Tenchurin, M. Pavlovsky, A. Shepelev, V. Mamagulashvilli, V. Gomzyak *et al*., *J*. *Phys*. *Conf*. *Ser*., **1347**, ID 012072 (2019)