Chapter 11
Application of Nanofiber-Based Composite: Progressive Health Impact

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11.1 Nanofibers Composite

Nowadays, nanofiber-based composite has appeared as the one of the important advanced materials that attract the attention of many researchers. By definition, nanofibers are Fiber with diameter range of 100 nm or less (Nayak et al. 2011). The very small fiber diameter of the nanofibers produces very large surface area per unit of volume (nanofibers ratio can be as large as 10^3 times of microfibers) (Abdul Rahman et al. 2014), good flexibility in surface functionalities (Haghi and Zaikov 2011) and superior surface properties that act as a platform for the binding sites to cell receptors (Huang et al. 2003). The fiber with micro-scale and macro-scale have been shown less effective for molecular and cellular applications compared to nano-scale fibers (Huang et al. 2003). These excellent properties of nanofibers make them to be broadly used in many medical applications such as drug delivery (Kanafi et al., 2019), tissue engineering (Pompa-Monroy et al. 2018), cancer therapy (Qiu et al. 2013; Wei et al. 2014), cell therapy (Wolfe et al. 2011) and regenerative medicine (Abrigo et al. 2015).

Nanofiber-based composite is a subset of nanocomposites. Nanocomposite is a material comprising more than one phases/components and at least one dimension of the structural phase in nanometric range (Sahay et al. 2012). In composite, the combination of two materials/phases is to produce a new material with desirable physical, chemical and/or biological property, which are significantly different from any of the constituent materials/phases. However, by comparison with conventional composites, the structure of nanocomposites affects their macroscopic properties and gives a great function. There are one or more discontinuous phase in composite

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that is called reinforcement and one continuous phase known as matrix (Shaohua et al. 2018). The reinforcing material can be fabricated of nanocomposite in zero, one or two-dimensional form (Mai and Yu 2006), which is usually stronger than the other material/phase as the name implies. Numerous studies have been done using the nanofiber-based composite and the results showed the mechanical properties and thermal/chemical stability that have been improved after incorporating nanofibers (Sahay et al. 2012; Paszkiewicz 2016; Komur et al. 2017; Pant et al. 2018; Park et al. 2019).

11.2 Classification of Nanofiber-Based Composite

Ramaligam and Ramakrishna (2017) classified nanofibers composite into three main categories according to matrix constituent, which are polymer matrix composites, ceramic matrix composites and metal matrix composites (Ramalingam and Ramakrishna 2017). The combination of a polymer matrix and a reinforcing matrix including carbon or glass is an example of polymer matrix composite (Ramalingam and Ramakrishna 2017). For instance, Xu et al. successfully synthesized PEO composite nanofiber mats using cellulose nanocrystals (CNCs) and cellulose nanofibers (CNFs) as reinforcement nanofillers (Xu et al. 2014). Ceramic matrix composite is a combination of ceramic matrix phase and a reinforcing ceramic phase (Ramalingam and Ramakrishna 2017). For example, highly environmental-resistant SiC/SiC composite has been strenuously performed using allylhydridopolycarbosilane (Li et al. 2012). The combination of metallic matrix phase with material other than metal such as ceramic or polymeric phase is known as the metal matrix composite (Ramalingam and Ramakrishna 2017). Biocompatible and antibacterial poly(ε-caprolactone)-nanosilver composite nanofibers scaffolds have been used for tissue engineering applications have a great potential in wound dressing applications (Sumitha et al. 2012).

11.3 Preparation Techniques

Nanofiber-based composite can be manufactured using various techniques such as electrospinning, template synthesis, self-assembly and phase separation. Electrospinning is considered as the most utilised method to produce polymer matrix composite nanofibers, possibly because it is a simple technique that can produce large-scale production of nanofibers, fast, can be applied to wide range of polymers besides the fiber diameter and pattern that are relatively easy to tune.

11.3.1 Electrospinning

Electrospinning is one of the most widely used techniques for polymer fibers. Polymer fibers can be produced by electrospinning technique with small diameter (Kong and Ziegler 2014) and uniform size of morphology (Dadvar et al. 2012). Nowadays, electrospinning technique has attracted much attention owing to its cost-effectiveness, appropriateness to a large variety of materials, goodness in controlling fiber morphology and its ability to be easily scaled. There are three important basic apparatus needed in electrospinning process, which are high voltage supply, collector and syringe pump (Fig. 11.1). To prepare polymer composite nanofibers, the polymer solution needs to be mixed with second materials until well dispersed. The metal needle fitted with syringe has to be filled with the solution on a syringe pump. The syringe pump slowly pumps out the solution; then, the needle is subjected into a high voltage. When the high voltage applied, the surface tension is reduced and the polymer droplet at the tip of metal needle transforms into a pointed shape. Increase in voltage supply will generate the Taylor cone formation and a jet from the tip of needle. When the solvent is jet travelled to the collector and form nanofibers, it will evaporate on the same time. To avoid the jet from turn into droplets (electrospraying), sufficient entanglement of polymer is required (Kong and Ziegler 2014).

Electrospinning is among the best techniques for nanofiber-based composite as it easily allows fabrication formation and can produce high yield of production (Ramalingam and Ramakrishna 2017). If the nanofiber-based composite involves paramagnetic, the magnetic nanoparticles will be directly mixed with polymer nanofibers. Surface treatment has been done in coating, salinization and grafting to avoid agglomeration to occur within matrices (Lee et al. 2015). For example, Fe_3O_4 nanoparticles can be directly mixed with polyvinylidene (PVdF) solution in dimethylacetamide (DMAc) and then, this mixed solution undergoes electrospinning to fabricate PVdF/Magnetite composite nanofibers composite (Russell and Venugopal

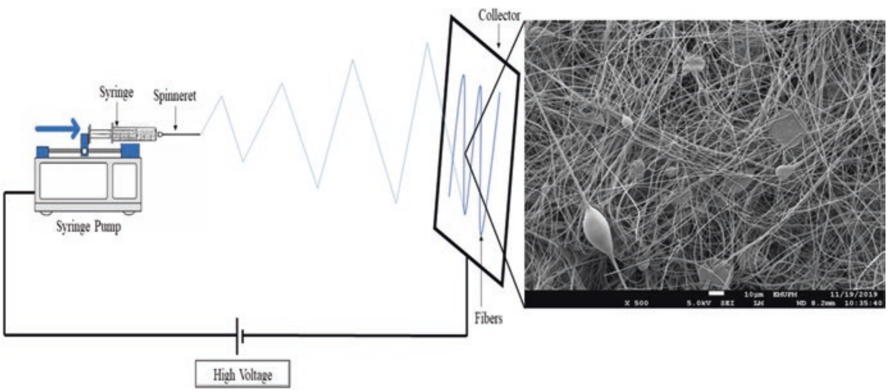

Fig. 11.1 Schematic diagram of electrospinning

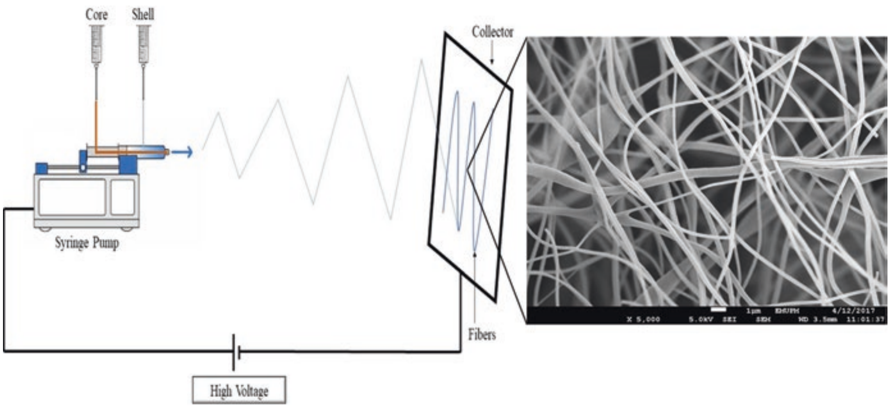

Fig. 11.2 Schematic diagram of coaxial electrospinning apparatus

2014). Electrospun ceramic composite fiber of aluminium acetate/polymer mixtures have been performed using electrospinning technique where the polymer used acted as a carrier for electrospinning purposes and was completely removed after the fiber was annealed at 1200 °C (Tuttle et al. 2008).

In advance technology, coaxial electrospinning has been used to fabricate the core shell nanofiber structures for particular applications. A schematic representation of coaxial electrospinning set up is shown in Fig. 11.2. Coaxial electrospinning is the extension and modification of electrospinning to produce polymer nanofibers with excellent core-sheath or hollow structures (Qu et al. 2013). The process of coaxial electrospinning and the electrospinning is almost the same; nevertheless, electrospinning process only use a single dispensing system to form a fiber on the collector, whereas two different dispensing methods are needed for coaxial electrospinning where the inner and outer fluids are fitted. This coaxial electrospinning technique is able to incorporate nonspinnable material into the phases of shell or core to turn into fiber form (Venugopal et al. 2010). In addition, the coaxial electrospinning can fabricate core-shell nanofiber (Ramalingam and Ramakrishna 2017). For instance, poly(ε-caprolactone) in a study has been dissolved in organic solvent 2,2,2-trifluoroethanol acting as shell solution while fluorescein isothiocyanate-conjugated bovine serum albumin was dissolved in deionised water and poly(ethylene glycol) act as core solution. After that, these shells outside the tube and core solution inside the tube were combined in electrospinning spinneret. It was then found that the nanostructure core-sheath composite nanofibers have achieved the desire product (Zhang et al. 2006) (Fig. 11.3). Nevertheless, electrospinning has some limitations including that it depends on high voltage power supply and low production rate (Abdal-hay et al. 2012a).

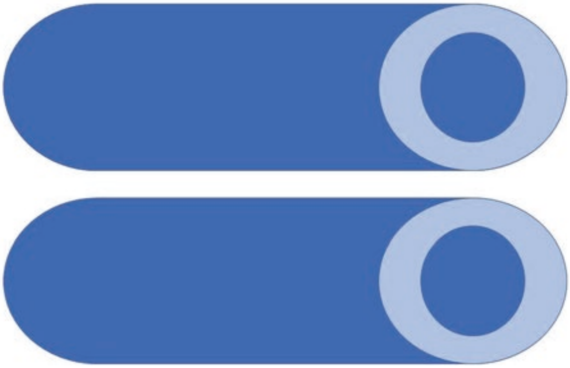

Fig. 11.3 Hollow composite nanofibers prepared by coaxial electrospinning technique

11.3.2 Air Jet Spinning

Air jet spinning is the one of the new techniques that can produce nanofibers with low cost, safe and ultra fast production rate. This technique is developed to overcome the problem from electrospinning technique. For air jet spinning technique, adjustment of the polymer concentration, distance between ground collector and the tip of nozzle are the factors controlling the diameter size of nanofibers. The air jet is invoked the surface tension of the polymer solution; thus, the solution of polymer is stretched into ultra thin fibers. At the same time, the solution vaporise from the product of nanofibers at the collector (Abdal-hay et al. 2012a). Polymer solution fed and pumped with air at high pressure is injected through an annular space around a small pipe. The ejection flow rate is controlled by needle. The polymer solution formed at the tip off the nozzle and the fast air jet stretch the polymer solution into nanofibers. The production of nanofibers takes place at the collector. The air jet spinning technique product is able to collect the nanofibers on solid or liquid collectors, which is similar with electrospinning technique, thus giving benefits to researchers for perform specific chemical or physical reaction on nanofibers product (Abdal-hay et al. 2012a).

This technique is excellent for producing all types of nanofiber composite as it is cheap to conformably and rapidly coat high yield on variety components. Extreme velocity is distributed by pressurised gas to form nanofibers at nozzle outlet and done until all fibers are deposited onto a substrate (Abdal-hay et al. 2012b). For example, nanohydroxyapatite/poly(lactic acid) (nHA/PLA) prepared by air jet spinning. Wet chemical precipitation method was used to synthesise the HA. Then, PLA solutions were dissolved in dichloromethane. Synthesized nHA was mixed with optimised PLA together to prepare suspension solution with continuous stirring followed by sonification of the colloids. Two colloidal solutions were prepared by nHA and PLA. These solutions were then deposited using custom design air brush spraying device. The operation was run at an optimised air pressure. The morphology was affected by variations of spraying distance. The samples were fabricated and dried in vacuum. Hydroxyapatite/poly(lactic acid) hybrid nanocomposite membrane was then formed (Abdal-hay et al. 2013).

11.3.3 Centrifugal Spinning

Centrifugal spinning technique is another method to produce nanofibers with numerous materials at low price and high speed. It is a simple and fast fabrication of nanofibers for many applications. The important components of centrifugal spinning technique are rotating spinning head and nanofiber collecting system. At a high rotating speed, two liquid jets are generated by centrifugal force at the same time from the needles connected to the syringes. Nanofibers collecting system is used to collect nanofibers in different forms. In centrifugal spinning, rotating spinning head place for the spinning fluid, which is punctured with multiple nozzles around the sidewall. When critical value of rotating speed is reached, the surface tension is overcome by centrifugal force to flow out a liquid jet from the nozzle top of the spinning head. The air frictional force and centrifugal force elongate the jets and undergo a stretching process. The fabrication of nanofibers is formed and deposited on the collector. Other forces that could be involved in this centrifugal spinning is surface tension, gravitational force and rheological force. The most important thing about this centrifugal spinning is that the production rate is high and beneficial for industry (Zhang and Lu 2014).

Centrifugal spinning can be used to prepare metal, ceramic and other composite material nanofibers due to its low-cost, environmental friendly and high spinning efficiency (Zou et al. 2014). For example, recycled bottle-grade poly(ethylene terephthalate), polystyrene and polypropylene were spun into fiber by melting using a centrifugal spinning technique. All recycled bottles were grinded and then each of ground were prepared. These polymers were added to orifice opening per spinneret. The heat was exposed to melt the polymer. The collector consisted of bars in circular pattern with some working distance. Fibers were formed by rotating the spinneret on the surface of collector and fully drew out the polymer from the spinneret (Zander et al. 2017).

11.3.4 Template Synthesis

Template synthesis is a simple technique and easy procedure that can fabricate the nanofibers in almost any laboratory. It is the requiring access to the devices of metal sputtering and electrochemical deposition (Ugo and Moretto 2007). In this method, hollow channels of porous ceramic or polymer templates are the places for producing nanofibers (Wu and Bein 1994). For the first step, the monomers are filled in the porous template. Then, the monomers in the hollow channels of the porous template produce the chemical or electrochemical polymer nanofibers. When the template is removed by dissolving or etching, the separated nanofibers are obtained. Most of nanofibers of template synthesis produced have a hollow structure because the synthesized polymer is prone to precipitate onto the inner surface of the hollow channels. The polymer solution can directly produce nanofibers and fed into hollow channel. The nanofibers are formed after the polymer solution is solidified, which removes the solvent. The diameter size of the nanofibers are larger compared to that of monomers preparation because polymer solution has high viscosity that will cause the hollow channel hard to be operated with small diameters. This technique can only produce a few micrometres long nanofibers. Membrane pore size is used to determine the diameter size of nanofibers (Zhang and Lu 2014). This technique is easy to utilise, which can adjust the particle size and morphology through template materials and is widely used for ceramic nanofibers composite as it has soft and hard templates; hard template can be used to synthesis the ceramic while the soft template is used to explore the combinations of inorganic and organic and propose a broad synthetic way (Xie et al. 2016).

11.3.5 Self-Assembly

Self-assembly technique is the method that produces nanofibers by holding small molecules together where the molecules arrange themselves into a structures or patterns using non-covalent forces such as hydrophobic forces, hydrogen bonding and electrostatic reaction (Beachley and Wen 2010). There are many mechanisms that can be employed to assemble nanofibers depending on the size of molecules. The most widely used mechanism on this technique is the formation of hydrogel that involves two interpenetrated phases, which are liquid phase and solid phase. Liquid phase usually uses water while solid phase is used in hydrogelator molecules to produce nanofibers (Yang and Xu 2007). Then, the liquid phase is removed from hydrogel and dried nanofibers are obtained. The disadvantage of this technique is that it is limited to small molecules that can self-assemble and arrange themselves under external stimulus. This technique also needs extremely long elaboration with low yield of production and cannot control fibers dimension (Li et al. 2007). For this technique, polymer nanofibers composite is widely utilised due to its clarity, high precision, cheap and high flexibility (Qi et al. 2018). Self-assemble technique can allow fast elaboration of nanocomposites that can integrated in sensors or films to modify microscopic properties. Firstly, silicon dioxide nanoparticles solution is dissolved in chloro-trimethyl-silane (CTS) and dried by solvent evaporation method known as salinization. Then, the nanoparticles bind on textiles where seven different solutions were used to bind with cotton textiles (Lopez-Barbosa and Osma 2017).

11.3.6 Phase Separation

The phase separation to produce nanofibers involves a few steps comprising polymer dissolution, drying, gelation, phase separation and solvent removal (Ma and Zhang 1999). For this preparation, the polymer needs to be dissolved to form homogenous solution at room or high temperature. The solution is kept at the gelation temperature until gel and phase separates are formed to form a nanofibrous matrix. The phases are separated because of the physical incompatibility. When the solvent is removed and the matrix is dried, the nanofibers are formed (Zhang and Lu 2014). The properties of nanofibers depend on polymer concentration; if the polymer concentration increase, the porosity of fibers decreases but with improved mechanical properties (Nune et al. 2017). Mechanical properties of nanofiber matrix can be changed by altering the concentration of the polymer (Ramakrishna et al. 2005). The disadvantage of using this technique is that the continuous fibers can be produced with short size, but not all polymers can use this technique as it needs gelation capability that is limited to only certain polymers (Alghoraibi 2018). The advantages are their porosity, charge density, hydrophilicity and thermal stability that may be adjusted by placing nanoparticles with definite elements and components on the surface or within the matrix of the polymer scaffold. The surface-located nanoparticles have excellent characteristics such as photocatalytic, adsorptive and antibacterial capabilities (Haase et al. 2017).

11.4 Application of Nanofiber-Based Composite in Biomedical Applications

Nowadays, nanofiber-based composite has been most widely used in biomedical applications including tissue engineering, drug delivery and gene delivery. The nanofiber composite offers many advantages and promising feature properties such as very high surface area per volume and designable flexibility in functionalisation of the fibers to form targeted product that can suit specific application.

11.4.1 Tissue Engineering

Biomimetic nanofiber scaffold mimicking with a great potential in the native extracellular matrix provides a good way to rebuild functions or achieve favourable responses for tissue regeneration. Nanofibers are now being used as scaffolds for cell infiltration and tissue growth. Electrospun nanofibrous scaffolds give promising achievement in cell attachment, penetration and proliferation (Goyal et al. 2013). In the tissue engineering field, the right choice of biomaterial as a substrate is very important for producing excellent scaffolds of fibrous materials. Among natural biomaterials, gelatine, collagen and chitosan are commonly used for skin regeneration (Naves et al. 2017). There are many biomolecules that are involved in this field to improve fibers functional properties for biomedical application. Growth factor (GFs) are naturally occurring substances capable of binding cell surface receptors and directing cellular activities for a new tissue regeneration (Varkey et al. 2004). Localised delivery of exogenous GFs is effective for healing process and cellular components formation, thus making them as a promising aspect for tissue regeneration (Chen et al. 2010a). Polymeric nanofiber scaffolds give appropriate microenvironment by action from extracellular matrix and growth factors promoting cell growth and tissue generation. For instance, hydroxyapatite/poly(lactic-*co*-glycolic) nanofibers scaffolds have been used in drug delivery system to promote osteoblast growth, proliferation and differentiation (Haider et al. 2014). Metallic nanofiber-based composites have been used to make it durable and has high antibacterial activity (Zahedi et al. 2009). Due to its excellent morphology, it can be used as ideal wound healing material, which involves large surface area that increases the efficiency of antibacterial properties (Williams et al. 2012). The nanofiber composite is also utilised in bone tissue engineering. For example, in the study by Lui et al. (Liu et al. 2009), nanofibrous gelatine with diameter 150 nm over apatite composite was studied regarding its the biomimetic behaviour and compare it with that of commercial gelatine foam.

11.4.2 Drug Delivery

The main aim for producing drug delivery is to develop efficient transport of drug molecules into the target tissues, cells or organs in the body for a certain period of time (Ramalingam and Ramakrishna 2017). It is dynamic and futuristic way for transporting the drugs in the medical therapy, which is not yet commercial until now. This drug delivery perhaps alter the desired properties and proper manner (Mohanty and Geetha 2017). Drug delivery system (DDS) has the potential to improve the existed drug (Webster 2006). The promising of therapeutic efficiency involves drug specificity, efficiency, tolerability and therapeutic index. The benchmarks for promising drug delivery are slow delivery, controlled release and targeted delivery. To design an efficient DDS, some factors need to be considered in terms of targeting ability, duration delivery, mechanism, nature of drug carrier, administration route, bioavailability, biocompatibility and drug characteristics. The polymeric nanoparticles or nanofibers, hydrogels, micelles and microspheres have an excellent property for drug delivery system. The gains from using these materials are from their low toxicity, enhanced drug targeting, improved therapeutic adsorption rates and good self-defence against any degradation reaction in the body (Safari and Zarnegar 2014).

Electrospinning is widely used for producing drug-loaded nanofibers due to its low cost, ease of handling, high encapsulation efficiency, high loading capacity and concurrent delivery of diverse therapies (Zamani et al. 2013). Usually, the drug molecules are delivered to target position by polymer nanofiber composites as candidate vehicle. Recently, nanofibers composite based titanium, which is a drug loaded nanofiber, has been studied for cancer chemotherapy. The titanium by the name of titanocene and PLLA nanofibers were studied to determine the efficiency of release system. The result of PLLA/titanocene composite fibers showed the best controlled release system for cancer chemotherapy (Chen et al. 2010b). In other study, Tran et al. (2015) demonstrated a controllable and switchable drug delivery of ibuprofen using poly(*N*-isopropylacryamide)(pNIPAM)/poly(ε-caprolactone) (PCL) depending on temperature responsive composite nanofibers. The ibuprofen was fabricated with three different types of nanofibers known as PCL, pNIPAM and pNIPAM/PCL composite nanofibers using electrospinning technique. Each nanofiber was tested on release rates at 22 °C and 34 °C. For PCL nanofibers, the ibuprofen was not affected with only 10% change in delivery rates while pNIPAM nanofibers were shown to quickly release the ibuprofen. Meanwhile, the pNIPAM/PCL nanofibers showed the best release rates of ibuprofen with linear and controlled release by 70% change in delivery at 22 °C and due to hydrophobicity of PCL and PNIPAM, this led to a lower release rates at 34 °C (Tran et al. 2015). Multiple drug delivery can be designed using nanofiber composite (Zhao et al. 2015). For instance, poly(ethylene glycol)(PEG)/poly($_L$-lactic acid)(PLA) nanofibers have been successfully loaded with two different drugs namely paclitaxel (PTX) and doxorubicin hydrochloride (DOX) for delivery system. The experiment was conducted to study their solubility properties and distribution in the nanofibers. The result showed DOX has a high release rate due to its high hydrophilicity that easily diffused into water, while PTX has low release rate due to its high hydrophobicity (Xu et al. 2009). A multi-layered electrospun nanofiber mesh is the time-engineered dual release system that is very useful in preparation when drug is release at different time. The drug to polymer ratio of every single mesh is designed as multilayer meshes. The control of release rate and duration of release of the drugs is depending on fiber diameter size and thickness of meshes (Wang et al. 2019).

11.4.3 Gene Delivery

Nanofiber-based composites are promising materials for emerging carrier system to deliver genes to the target sites. Gene delivery technologies can improve the functionalisation of the target. Appropriate carrier system, nontoxic, ability to overcome immune responses and ability to go through complicated reaction in the body to reach the target site are the important factor for gene delivery of clinically valuable cell types such as stem and cancer cells (Sung et al. 2003; Panyam and Labhasetwar 2003). Viral and nonviral vectors are categorised as gene delivery vehicles. It has been revealed that direct view of viral based vectors in the human body can cause immune responses to become bad. Thus, several studies have been done to fix gene delivery with biomaterial system (Jang et al. 2007). The gene delivery response to the target tissue relies on the delivery mechanisms such as receptor mediated endocytosis, delivery mode and nanofiber material properties including biodegradability and bioavailability (Xiang et al. 2011).

The electrospun nanofiber composites is used as spatial templates to make it efficient in altering the functions of native extracellular matrix (Sill and von Recum 2008). Electrospinning and coaxial electrospinning are cost effective for producing nanofibers for gene delivery. Usually, nanofiber composites consist of ceramic or polymer. The genes also mix with polymer solution to embed themselves into nanofibers and immobilised into the target genes through nanofibers (Lakshmi Priya et al. 2017). For example, the electrospun poly(*L*-lactic acid)/collagen nanofiber composite has been used for bone morphogenetic protein plasmid DNA delivery and the result showed that the bone was greatly formed (Zhao et al. 2016). The DNA was successfully embedded into porous composite structures to utilise the encoded growth factors, signalling molecules and other bioactive molecules (Lee et al. 2014).

11.5 Conclusions and Future Remarks

Nanofiber composites are a new class of nanomaterials that have gained attention due to its outstanding structural and tunable physical properties, which is usually superior compared to their individual parent materials. Significant progress has been made by researchers to produce new nanofiber composite. New materials, systems, processes, and formulations are being developed to solve problems and to create new potential application of the nanofiber composite. Nanofiber composites prepared of biocompatible and biodegradable materials show great potential in biomedical applications such as wound healing, tissue engineering, cancer therapy, stem cells, and drug delivery. Although nanofiber composites were used effectively for the biomedical field, the applicability of the fibers could be enhanced. Nanofiber composites are expected to give big impact in wide range of biomedical applications, with great challenges and expectations ahead.

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