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# SideroGuard: Overview of Siderophore-Enhanced Nanofiber Systems for Biofilm Prevention and Control

Sitalakshmi Thyagarajan<sup>a,\*</sup>, Senthamil Selvi Poongavanam<sup>b,\*</sup>

<sup>a</sup> Department of Bioinformatics, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences (SIMATS), Thandalam, Chennai-602105, Tamil Nadu, India.

<sup>b</sup> Nano biomedicine Lab, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai - 602105, Tamil Nadu, India

\*Corresponding author: [sitalakshmit@gmail.com](mailto:sitalakshmit@gmail.com) (ST)

## Abstract

In recent years, there has been an incredible increase in scientific innovation in curing biofilms on chronic wounds. Microbial biofilm is an aggregate of microbial cells surrounded by a polymer matrix that may or may not adhere to surfaces, but present in the tissues or secretions. The free iron involves in biofilm formation, delayed wound healing, and may even be responsible for destruction of connective tissue. To minimize the free iron on wound sites to avoid biofilm formation, the use of siderophores and their derivatives were focused. To address this requirement, researchers have developed various techniques such as non-electrospinning and electrospinning techniques for the formation of nanofibers. Electrospinning has confirmed to be an excellent method for the fabrication of nanofibers which gained the interest of biomedical applications. Electrospinning is a current technique in which electric fields are used to produce fine fibers wherein diameter can be reduced to nanometers which has wide application in the field of medicine. The review aims to discuss the importance of electrospun siderophore-based nanofibers as nanohealers for wound biofilm formation.

**Keywords:** Siderophore, Electrospinning, Nanofibers, Biofilms, Chronic Wounds



## 1. Introduction

A wound is a damage to the body's tissues, involving in breaking of skin or underlying structures. Wounds vary in severity, from minor scrapes to more serious injuries like lacerations, puncture wounds, or burns. The causes of wounds can include accidents, trauma, surgical procedures, or medical conditions (1,2). During the past few decades, despite advancements in therapies and wound dressing, the prevalence of chronic wounds continues to rise, especially among populations with conditions like diabetes mellitus or those undergoing immunosuppressive treatments and biofilm formation of the wound regions. Chronic wounds fail to heal, in the expected time which might take a couple of weeks in some cases (3–6). Alterations of cytokines, growth factors and ECM components at the wound site may also lead to the formation of chronic wounds. Moreover, factors like oxidative damage of free radicals, infection, ischemia and the accumulation of necrotic tissue are also other causes of many non-healing wounds (7,8). Several studies have demonstrated that increased levels of microbial load and microbial biofilm formation distinguish chronic wounds (9). It's evident that biofilm-related issues pose significant challenges in wound healing and connecting the gap between laboratory research and clinical practice is crucial for improving patient outcomes (10–14). While the field lacks a clear standard of clinical practice, several promising strategies are being explored for biofilm management (15). These strategies help to study the advantages and limitations of electrospun nanofibers (11,16). This paper highlights the importance of microbial siderophore nanofibers as effective nanohealers for biofilm formation.

## 2. Importance of biofilm in wound healing

Biofilms were first reported as animalcules by Anton von Leeuwenhoek. But later it was observed as a suitable surface that facilitates microbial growth wherein, the biological activities were greatly accelerated. Studies on microbial varieties revealed the physical arrangement of the shiny layer which was later named “slime” paved the way for a wider perspective of biofilm interaction. Bill Costerton in 2002 was the first to coin the term “biofilm” which was described as group of microorganisms covered within a self-produced matrix of extracellular polymeric substances (EPS)(17). Extracellular Polymeric Substances are produced by microorganisms to form a defensive and supportive structure around themselves. It is made up of polysaccharides, proteins, nucleic acids, lipids, and other macromolecules. The composition also varies for

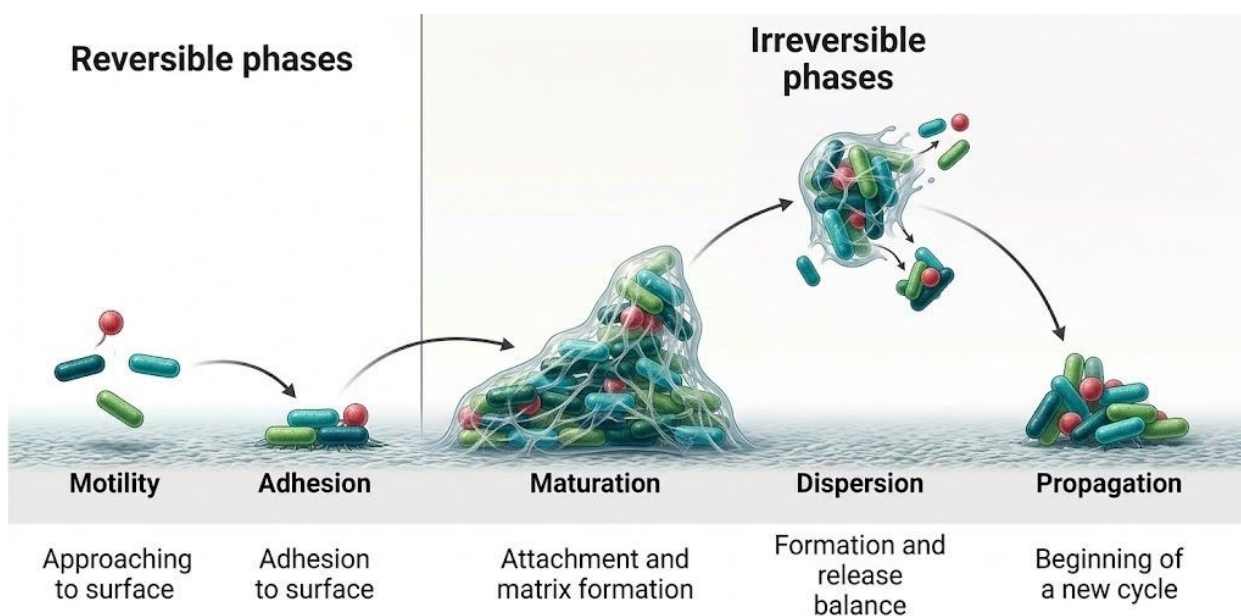


microbial species in relation to environmental conditions, and the stage of biofilm development. This biofilm mainly protects the bacteria from the host immune response and environmental factors like antibiotics, disinfectants, and dehydration. This resistance makes it challenging to eradicate the bacteria causing chronic wounds. Biofilm offers a habitat for microorganisms by establishing a protective environment against the host. Microbes existing in biofilms are more resistant to antibiotics because of gene transfer which provides inter-cellular communication and encourages growth. Biofilm bacteria release the toxins and enzymes that damage host tissues and interfere with cellular signaling pathways involved in wound repair. Chronic inflammation caused by persistent infection further delays healing. Biofilm-associated infections are often recalcitrant to conventional treatments. Traditional antibiotics are less effective against biofilm bacteria due to their limited penetration into the biofilm matrix and the presence of dormant cells within the biofilm (17–19).

Iron plays a vital role in multiple stages of biofilm formation by acting as an important regulator of microbial metabolism, adhesion, quorum sensing, and extracellular polymeric substance (EPS) production. During the initial stage (stage 1–2), iron exists predominantly as ferric iron ( $\text{Fe}^{3+}$ ) bound to host proteins such as transferrin, ferritin, and heme-containing molecules released from damaged tissue. The Surface-associated  $\text{Fe}^{3+}$  increases microbial attachment thereby increase electrostatic interactions between bacterial cell surfaces and host extracellular matrix components. Several pathogens, including *Pseudomonas aeruginosa* and *Staphylococcus aureus*, sense iron availability via iron-responsive regulatory systems (e.g., Fur regulon), which upregulate adhesins and surface proteins essential for irreversible attachment (20,21). During the stage -3 the microcolony formation occurs which requires iron for as a metabolic cofactor, DNA synthesis, respiration, redox homeostasis. At this stage, bacteria actively secrete siderophores which are high-affinity chelators that specifically bind  $\text{Fe}^{3+}$  from host sources. The iron–siderophore complexes are transported into the bacterial cell through specific outer membrane receptors which supports rapid cell division and also facilitates interspecies competition, as siderophore production limits iron availability to competing microbes, thereby shaping biofilm community structure(22–24). At the of stage 4–5, iron availability directly acts on EPS synthesis and biofilm architecture wherein the elevated levels of  $\text{Fe}^{3+}$  stimulate the production of polysaccharides such as alginate, Psl, and Pel, which increase biofilm thickness and mechanical stability. Iron also promotes quorum sensing–mediated gene expression, and increases the coordinated biofilm behaviors including



virulence factor secretion and stress tolerance. In mature biofilms iron undergoes redox cycling between  $\text{Fe}^{3+}$  and ferrous iron ( $\text{Fe}^{2+}$ ) particularly in chronic wounds.  $\text{Fe}^{2+}$  generates reactive oxygen species (ROS) which cause host tissue damage and further impair wound healing, while biofilm bacteria remain protected within the EPS matrix (24). In stage 6, iron limitation, often induced by host sequestration mechanisms or therapeutic chelation which downregulates EPS synthesis and promotes motility and planktonic behaviour, facilitating dissemination to new sites. Microbial siderophores such as pyoverdine, Enterobactin, and Desferrioxamine form stable complexes with  $\text{Fe}^{3+}$  by removing iron from host proteins. Incorporation of siderophore-based systems into wound dressings exploits this mechanism by sequestering free ferric iron at the wound site, thereby reduce biofilm-forming bacteria of an essential micronutrient. This iron restriction disrupts biofilm establishment, reduces EPS production, attenuates virulence, and increase the bacterial susceptibility to host immune defence and antimicrobial agents.



**Fig.1.** Stages of biofilm formation highlighting iron-dependent maturation relevant to chronic wound environments. Reproduced from Ref. [9] with permission from Frontiers, copyright 2022.

The stages of biofilm are summarized in Fig.1. The more mature biofilms are heterogeneous, having characteristics similar to those of multicellular organisms. Studies reported that formation of biofilms is mainly attributed to the presence of free iron which leads to connective tissue destruction. Iron is an essential micronutrient for cellular processes; however, excess of free iron can pose unique challenges in delaying wound healing(12,13).



Iron chelators incorporated in the wound dressing materials may hasten the wound healing. Studies reveal that Lactoferrin, an iron chelator in mammals inhibit the formation of biofilms. Similar reports were obtained with synthetic iron chelators (13). The use of microbial siderophore as an iron chelator regulates the biofilm formation. The research reports suggest that incorporation of siderophore-based nanofibers for wound dressings controls the bacterial growth and biofilm formation on chronic wounds (25).

### 3. Consensus for management of biofilms

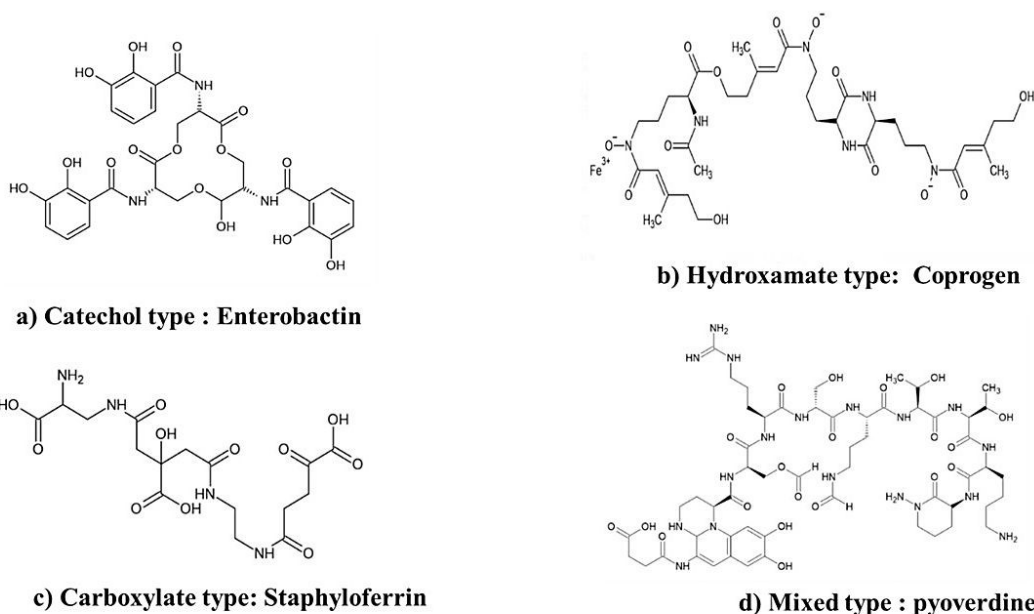
Control of biofilms on the wound sites involves a complex method due to their flexibility and capability to resist traditional treatments. The prevention of biofilm is often more effective than treating established biofilms which involves in maintaining good hygiene practices, proper sterilization procedures, and regular cleaning of surfaces to remove biofilm precursors (25). The mechanical methods like brushing, scraping, or flushing, physically disrupt biofilms and are effective for biofilms on surfaces like teeth, medical implants, or industrial equipment (15). The chemical agents are used to break down the biofilm matrix and kills the embedded bacteria which includes enzymes, surfactants, chelating agents, and disinfectants. However, selection of an appropriate agent is crucial as these biofilms are resistant to many antimicrobial compounds. Antibiotics or antimicrobial agents are used to target bacteria within the biofilm (13,16). However, penetration of these agents into the biofilm matrix are limited, and bacteria within biofilms often exhibit increased resistance to antibiotics compared to planktonic (free-floating) bacteria. By combining the different approaches, like physical removal with chemical disruption or antimicrobial therapy, reduce the risk of resistance development. In some cases, using materials that resist biofilm formation can be beneficial (2,16,17). For example, certain coatings or surface modifications discourage bacterial attachment and biofilm formation. One such modification includes the use of microbial siderophore nanofibers as biofilm inhibitors (17). The microbial siderophores hunts the iron components and disrupt the biofilm formation on the wounds. This biofilm wound care is an effective approach to biofilm management which enhances the reduction of microbial load and biofilm burden at the wound sites (18,19).

### 4. Microbial siderophore types and their chemistry

The types of siderophores are based on the chemical group utilization for iron coordination, leading to three primary classes: catecholates, hydroxamates, and ( $\alpha$ -hydroxy-) carboxylates, with



a fourth "Mixed type" incorporating combinations of these groups Fig.2. Catecholate siderophores are a class of siderophores mainly produced by bacteria which contains either mono or dihydroxybenzoic acid residues, which are utilized to chelate iron. These residues are obtained from dihydroxybenzoic acid (20,21). The two main types of catecholate siderophores include monocatecholates, wherein these siderophores contain a single dihydroxybenzoic acid residue used for ferric iron chelation and dicarboxylates siderophores feature two dihydroxybenzoic acid residues for ferric iron binding. Enterobactin is the most well-known example of catecholate siderophores, which fall under the dicarboxylate type (20,22). The hydroxamate siderophores are another class involved in iron acquisition, characterized by hydroxamic acid groups used for ferric iron chelation. These hydroxamic acid were typically derived from amines like lysine or ornithine. There are two main types of hydroxamate siderophores namely monohydroxamate and dihydroxamate (23).



**Fig. 2.** Structural classification of siderophores and their iron-chelating relevance in biofilm inhibition.

The monohydroxamate siderophores mainly contains single hydroxamic acid group used for iron chelation. These siderophores naturally contain one hydroxamic acid moiety derivative from amino acids such as lysine or ornithine. The examples of monohydroxamate siderophores include ferrichrome, which is produced by various fungi and certain bacteria, for example the



monohydroxamate rhizobactin 1021 were produced by rhizobia bacteria. These siderophores show a vital role in iron acquisition and are vital for the existence and virulence of many microorganisms. The dihydroxamate siderophores contains two hydroxamic acid groups used for iron chelation. These siderophores contain two hydroxamic acid moieties derived from amino acids such as lysine or ornithine (23). The examples of dihydroxamate siderophores include aerobactin, schizokinen, and alcaligin. Aerobactin is produced by various Gram-negative bacteria which are associated with virulence in certain pathogens. Schizokinen type siderophores are produced by soil-dwelling plant symbionts, while alcaligin type siderophore is produced by certain bacteria and is involved in iron acquisition in both host-associated and environmental contexts. The carboxylate type is characterized by the presence of carboxyl functional groups, which act as oxygen donor atoms to bind iron.

The examples of carboxylate siderophores includes rhizobactin DM415, staphyloferrin A and B, vibrioferrin, fungal rhizoferrin, and bacterial rhizoferrin (24). The mixed-type siderophores are a different class of siderophores which incorporates the different chemical groups for iron chelation. Unlike single-class siderophores like catecholates, hydroxamates, or carboxylates, mixed-type siderophores utilizes the mixture of these groups in their structure(22,23). These class of siderophores determines the versatility of iron coordination, potentially enhancing their efficacy in iron acquisition. However, specific examples and features of mixed-type siderophores vary widely due to their diverse chemical compositions and structural variations (24).

### **5. Siderophore: Natural iron chelators as a biofilm inhibitor**

The history of siderophores is so fascinating for several decades of scientific inquiry and discovery. Siderophores were first discovered in the mid-20th century when researchers observed that microorganisms, particularly bacteria, and fungi, secreted compounds to scavenge iron from their environment. These compounds were termed siderophore ("sidero" for iron and "phore" for carrier) which have small organic molecules with a high affinity for iron to acquire iron from their environment. The siderophores bind tightly to iron ions, forming stable complexes that can be observed by the microbes through the specific transport system on the cell membranes, effectively "stealing" iron from their environment (26). The research work by Jacques Monod and Andre Lwoffon in 1950s revealed that the siderophore produced by microbes to scavenge iron from their surrounding and help them to transport it into the cell, which are very important for their survival



and growth (27). As research progressed, the biological significance of siderophores became increasingly evident and found to play crucial roles in microbial iron acquisition and also in various ecological processes, including competition between microorganisms for limited iron resources.

Siderophore has drawn attraction to their function in microbial physiology because of their uses in environmental remediation, biotechnology, and medicine. Siderophore-based strategies, have been found to improve wound healing applications and function as innovative antimicrobial agents that target the iron metabolism of bacteria (28). In recent years, siderophores research had continued more than a decade, with a focus on uncovering novel siderophores, explaining their roles in microbial communities, and discovering their latent therapeutic applications, including as antimicrobial agents or as carriers for controlling biofilm formation. The research reports had revealed that Enterobactin (siderophore) produced by *E.coli* were subjected to extensive investigation due to its remarkable ability to bind iron. Its structure features have three catecholate units arranged in C3 symmetry, branching from a chiral triserine lactone backbone. The metal binding units, of siderophore play pivotal roles in forming metal binding complexes was highlighted by the research studies of Pollack et al. in 1970. The macrocyclic structure of the siderophore backbone was elucidated and provided a preorganization that enhances its metal binding ability. which lowers the pH and reducing proton competition, thereby facilitating stable complex formation. The ability of siderophore to form stable complexes with metals had encouraged researchers to explore their potential applications in wound applications (28). Certain research studies reveal that these stable complexes would deplete the availability of iron in the wound area paving a way to reduce the biofilm formation. By harnessing its metal binding capabilities, siderophore holds promise for novel approaches in eliminating the microbial load on wound regions and also eradicating biofilm formation (29). Combining electrospinning with siderophores could involve incorporating siderophores into the polymer solution or melting before electrospinning. This result in the production of nanofibers with siderophores immobilized within the polymer matrix. These nanofibers can be used to capture metal ions from aqueous solutions or as components in wound dressings or tissue engineering scaffolds with enhanced biofilm inhibitor properties due to the iron-chelating ability of siderophores. This approach needs a careful analysis of the compatibility between the siderophores and the polymer used for electrospinning, as well as optimization of the electrospinning process to ensure uniform distribution of the siderophores (30).



## 6. Microbial siderophore focus and targeting on biofilm formation

As iron-chelating molecules, siderophores plays an important role in biofilm formation, affecting microbial survival. These molecules scavenge iron from the environment, limiting the bacteria in biofilm of these essential nutrients. By limiting iron availability, siderophores can delay the initial attachment of bacteria to surfaces and consequent biofilm development. At lower concentrations, siderophores primarily inhibit initial bacterial attachment and early biofilm development, while higher concentrations disrupt biofilm maturation, EPS production, and quorum sensing–regulated pathways. Their antibiofilm efficacy is most pronounced under iron-limited conditions, closely resembling host environments. Siderophores also influence bacterial communication systems like quorum sensing, which directs the biofilm formation (31–34). Quorum sensing depends on signaling molecule production and detection to co-ordinate microbial activities such as biofilm growth. Siderophore disrupts the quorum sensing pathways, affecting biofilm formation or structure (34).

As iron-chelating molecules, siderophores plays an important role in biofilm formation, affecting microbial survival by scavenging iron from the environment and limiting the bacteria in biofilm environment. By reducing iron availability, siderophores can delay the initial attachment of bacteria to surfaces and consequent biofilm development. At lower concentrations, siderophore inhibit initial bacterial attachment while at higher concentrations they exhibit the disruption of biofilm maturation, EPS production, and quorum sensing–regulated pathways. Their antibiofilm efficacy is most pronounced under iron-limited conditions, closely resembling host environments. Siderophores also influence bacterial communication systems like quorum sensing, which directs the biofilm formation (31–33). Quorum sensing depends on signaling molecule production and detection to co-ordinate microbial activities such as biofilm growth. Siderophore disrupts the quorum sensing pathways, affecting biofilm formation or structure (34).

In the host environment, iron is tightly controlled as part of nutritional immunity to restrict microbial growth. Pathogenic bacteria-produced siderophores can compete with host iron-binding proteins for iron uptake. The spectrum of activity of siderophores is broad but variable. In bacterial biofilm siderophore can alter the microbial composition and dynamics, causing changes in biofilm structure and their stability. According to various research investigations, it is reported that siderophore-mediated iron uptake is mostly responsible for the antibiofilm activities against Gram-



negative bacteria such *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Escherichia coli*. Siderophores affect competition and biofilm stability in polymicrobial biofilms by changing the availability of iron. Bacteria manage the host defenses and promote the production of biofilms in host tissues through siderophore-mediated iron uptake. Interactions among the different microbial species are important for biofilm formation influencing interspecies interactions by modulating the iron availability and microbial competition within the biofilm community (35).

Compared with traditional antibiotics these siderophores function as anti-virulence agents by limiting iron thereby killing bacteria and lowering the selective pressure for resistance while exhibiting limited effectiveness against mature biofilms. Siderophores exhibit better biocompatibility and higher iron selectivity than the metal chelators like EDTA, which may unintentionally promote the growth of infections that use siderophores. The quorum sensing inhibitors shows a dual effect on iron metabolism and cell–cell signaling their activity is influenced by environmental iron levels.

Electrospinning nanofiber incorporated with siderophore compounds have good potential to offer numerous benefits wherein these nanofibers physically disrupt the structure of biofilms and making them more susceptible to treatment (36). The siderophores present in the nanofibers chelate iron ions, depriving the biofilm-forming bacteria of their essential nutrient and inhibiting their growth and biofilm formation (37,38). By targeting iron chelation, these nanofibers have a good potential to interfere with bacterial virulence, reducing their pathogenicity and the severity of infections (38).

These siderophores show a promising strategy for antibiofilm control, particularly when it is incorporated into nanofiber-based delivery systems and also when used in combination with antibiotics or enzymatic agents. Their ability to target iron-dependent virulence pathways shows a biologically relevant approach to manage biofilm-associated infections and also recognizing the need for optimized dosing and combination therapies. This approach proves to be more valuable in biofilm-related infections, which often focus on conventional antimicrobial therapies due to the protective nature of the biofilm matrix (39).

## 7. Medicated nanofibers for biofilm healing

Medicated nanofibers provide an excellent platform for studying biofilm formation. Their properties make them ideal substrates for mimicking various surfaces encountered in medical





polyacrylonitrile (PAN), polyvinyl alcohol (PVA), polyethylene oxide (PEO), polycaprolactone (PCL), and polylactic acid (PLA) are frequently used due to their flexibility and tunable properties (45,46). Proteins like collagen or gelatin serve as a fundamental building block in the human body, making up a significant portion of connective tissues such as skin, bones, tendons, and ligaments. It provides structural support, elasticity, and strength to various tissues and organs (47,48). In recent years, collagen has gained significant attention in the field of nanofibers research and applications. Nanofibers made from collagen offer several advantages namely biocompatibility and biomimic properties providing an ideal environment for cell adhesion, proliferation, and cell differentiation (49). Certain biopolymers like cellulose, chitosan, and silk fibroin are used for their sustainability (50)[51]. The production of nanofibers can be achieved through various techniques and one such recent technique is application of electrospinning which offers unique advantages and is suitable for different applications in the field of medicine Fig. 3.(51,52).

### 8. Fabrication of siderophore-loaded nanofibers

Fabrication of siderophore-loaded nanofibers involves several key steps, which are important in ensuring the successful integration of siderophores into the nanofiber matrix and the production of fibres with desirable properties (53). The choice of polymer is important for the fabrication of siderophore-loaded nanofibers. The commonly used polymers include PVA, PCL and PEO, where these polymers are used for fabrication of siderophore-loaded nanofibers through electrospinning which is a promising technique for biofilm management (32). These fibers are used in medical, industrial, and environmental applications, offering a novel method to prevent biofilm formation (48). The fabrication of siderophore-loaded nanofibers using PCL by electrospinning is a suitable technique for biofilm management. PCL is a biodegradable polymer known for its excellent mechanical properties and biocompatibility and making it suitable for fabricating siderophore-loaded nanofibers for biofilm applications. These fibres have a good potential in the field of medical, industrial, and environmental applications and offers a novel method to prevent biofilm formation (41,42).

Polyethylene Oxide (PEO) are water-soluble polymer which known for biocompatibility and non-toxicity and making it an excellent candidate for fabricating siderophore-loaded nanofibers for biofilm applications. The fabrication of siderophore-loaded nanofibers using PEO via electrospinning is a promising technique for biofilm management. These fibers hold significant



potential in medical, industrial, and environmental applications, offering a novel method to disrupt and prevent biofilm formation(42).

### 9. Electrospun nanofibers as a nanohealers

Electrospinning has become progressively fascinating in recent decades, by attracting much attention to versatility and extensive applicability, particularly within disciplines such as biomaterials science, and nanotechnology (54). Electrospinning has its roots in the early 20th century (39,47). In 1902, British engineer Sir William Thomson (also known as Lord Kelvin) patented a method for the electrostatic spinning of fibers. However, it wasn't until the 1930s that further progresses were made (35,49). In the 1930s, Anton Formhals, an American physicist, made an important contribution to the progress of electrospinning technology (39,55). He developed a method for producing ultra-fine fibers using electrostatic forces. The research work of Formhal *et al.* work also laid a good the foundation for modern electrospinning techniques in mid-20th century (54,55). During this period, researchers discovered various aspects of the process, including the effects of different parameters such as voltage, polymer solution properties, and collector configurations on fiber morphology (39,56). This development gained its importance in late 1990s and early 2000s in the field of materials science and nanotechnology for various applications (55,57,58). Researchers began to explore the potential of electrospinning for producing nanoscale fibers with detailed control over their properties. In the past few decades, electrospinning shown a rapid progress by developing coaxial electrospinning and near-field electrospinning to enhance the versatility and capabilities of the process(39,59,60). The history of electrospinning shows (Table 1) the journey of investigation, innovation and technological advancement, with each milestone by contributing to our understanding of the process and expanding its potential applications.

The electrospinning setup comprises key components such as a syringe pump, a high-voltage power supply, and a metal collecting plate(61,62). The syringe pump directs a consistent flow of polymer solution, while a high voltage generates an electrically charged polymer jet from the nozzle. The setup generates an electric field at the nozzle, typically 1 to 50 kV per meter, initiating the process and also leads to electrostatic repulsion forces to overcome the liquid's surface tension, collecting high-voltage electrical charges and also the liquid reforms into a cone formation known as the Taylor cone, expelling a charged jet from its tip (56,61,62). The trajectory of the jet experiences bending variabilities which leads to whipping and oscillation as it progresses.

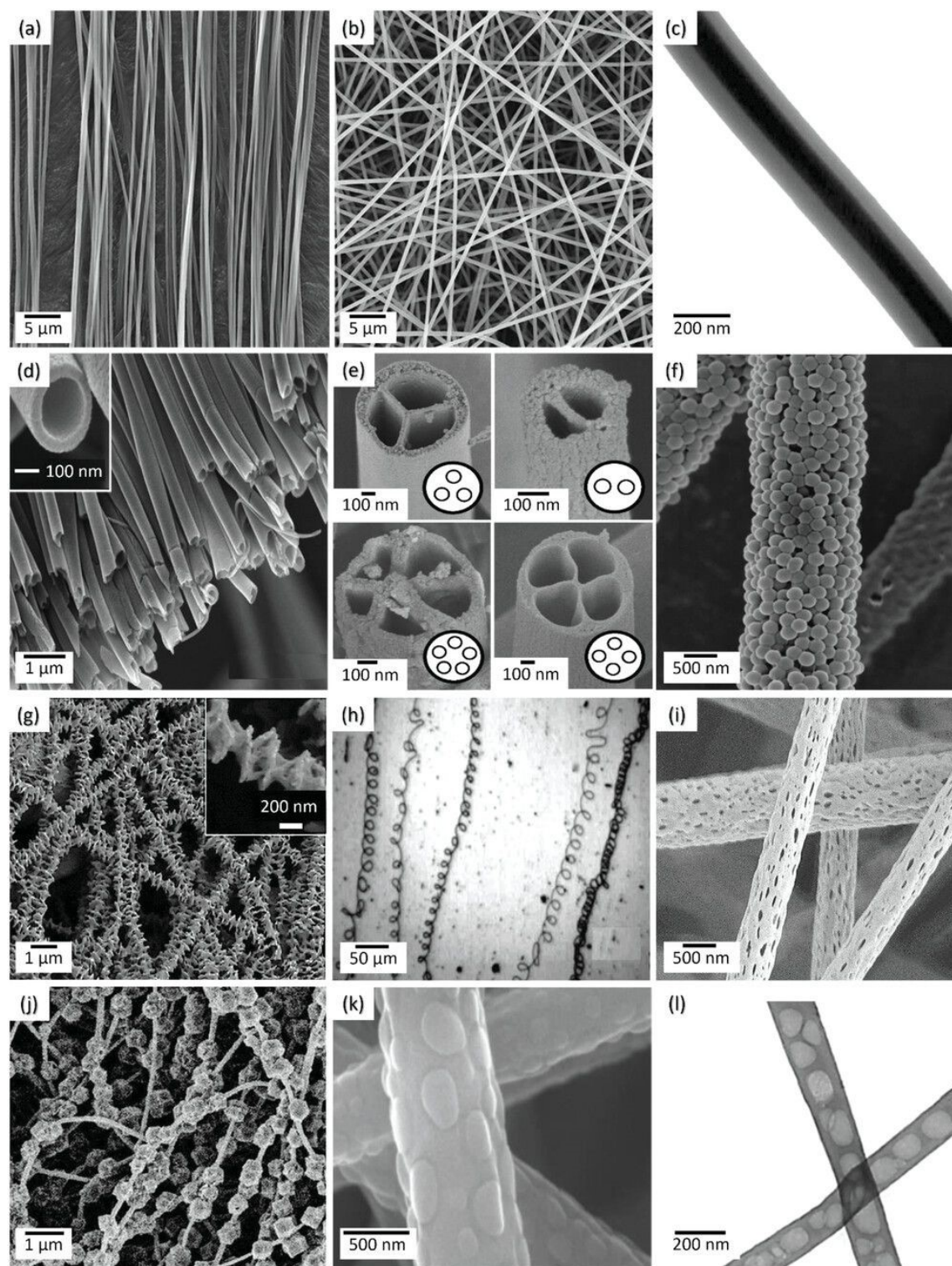


As the jet stretches into thinner diameters, it swiftly solidifies, depositing solid fibers onto a grounded collector plate. Various collector designs like plates, drums, mandrels, and discs, can be utilized. In some cases, residual solvent may remain in the nanofibrous mat, imposing post-processing adjustments (54,56).

**Table 1. The Evolution of Electrospinning: Landmark Discoveries and Technological Advances**

Types	Inventors & Year	Applications	Ref.
Mono-axial	Cooley and Morton (1902)	Drug delivery	(52)
Co-axial	Sun et.al (2003)	Modelling Drug Release	(63)
Multi-jet	Ding et.al (2004)	Nanosensors	(64)
Magnetic field	Yarin et.al (2004)	Textile Industries	(65)
Roller	Jirsak et.al (2005)	Skin Tissue Engineering	(66)
Porous tube	Dosunmu et.al (2006)	Waste Water Treatment	(67)
Bubble	Liu et.al (2008)	Therapeutic and Diagnostic tools	(68)
Tri-axial	Kalra et.al (2009)	Loading of Multiple Drugs	(69)
Ball	Miloh et.al (2009)	Water Purification	(70)
Disk	Niu et.al (2009)	Drug delivery	(71)
Wet 3D	Yokoyama et.al (2009)	Waste Water Treatment	(72)
Cone	Lu et.al (2010)	Biomedical and Food Applications	(73)
Spiral Coil	Wang et.al (2012)	Electrodes For Batteries	(74)
Beaded Chain	Liu et.al (2008)	Energy Catalysis	(68)
Cold Plate3D	Sheikh et.al (2015)	Skin Damage and Diabetic Ulcers	(50)
3 Dimensional	Vong et.al (2018)	Cell infiltration and Wound Healing	(61)





**Fig. 4.** Various structure of electrospun fiber morphologies: (a) aligned, (b) randomly oriented, (c) core/shell, (d) hollow, (e) multi-channel microtubes, (f) colloidal nanoparticle-decorated, (g) shish-kebab, (h) helical, (i) porous, (j) necklace-like, and (k) island-like. (a-c, i) Reproduced from



Ref. [75] with permission from Wiley-VCH GmbH, copyright 2023, (d) Reproduced from Ref. [81] with permission from Wiley-VCH GmbH, copyright 2023, (e) Reproduced from Ref. [55] with permission from American Chemical Society, copyright 2017, (f) Reproduced from Ref. [76] with permission from American Chemical Society, copyright 2012, (g) Reproduced from Ref. [77] with permission from American Chemical Society, copyright 2013, (h) Reproduced from Ref. [78] with permission from Elsevier, copyright 2008, (j) Reproduced from Ref. [80] with permission from Royal Society of Chemistry, copyright 2021, (k) Reproduced from Ref. [79] with permission from American Chemical Society, copyright 2017, and (l) Reproduced from Ref.[59] with permission from Springer Nature, copyright 2020.

The electrospinning process includes charging a liquid droplet with electricity, forming a Taylor cone or cone-shaped jet, extending the jet in a straight path, thinning the jet using an electric field, increasing electrical bending instability (also known as whipping instability), and ultimately solidifying and collecting the jet as solid fibers on a grounded collector. The electrospinning process involves charging a liquid droplet with electricity, forming a Taylor cone or cone-shaped jet, extending the jet in a straight path, thinning the jet using an electric field, increasing electrical bending instability (also known as whipping instability), and ultimately solidifying and collecting the jet as solid fibers on a grounded collector. Among the various morphologies shown in Fig. 4, porous and core-shell nanofibers are particularly suitable for siderophore delivery and sustained iron chelation in wound environments (55). Different polymer matrices exhibit distinct physicochemical and biological properties that influence siderophore loading efficiency, release behavior, and antibiofilm performance (55,59,75–81).

## 10. Current investigations and future directions

The preparation of nanofibers from microbial siderophore by electrospinning process gain a positive approach in addressing the challenges related to biofilms. Their ability to interrupt the biofilm and also the combined benefits of electrospinning technology, makes them suitable for various applications, like healing medical wounds and also preventing industrial biofilms (23,82). According to research reports, the stability of nanofibers leads to increased degradation of biofilms at wound sites. Since siderophores occur naturally, the biocompatibility of the entire nanofiber system confirms their safety for medical use. It is important to develop electrospinning processes that are cost-effective and scalable for the commercialization of nanofibers loaded with siderophores.



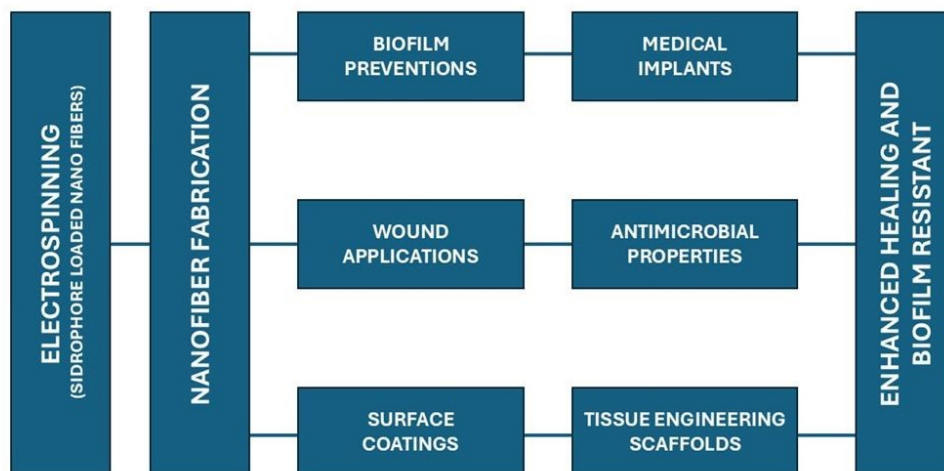
Biphasic scaffolds prepared from the University of Nebraska was a fascinating method in drug delivery and antimicrobial therapy(72,83). The researchers combined the nanofiber mats with microneedle arrays and developed a delivery system to target bacterial biofilms. The usage of coaxial type to make the scaffolds had a good control over the structure thereby enhancing the transfer of antimicrobial agents. The use of polyvinylpyrrolidone (PVP) microneedle arrays and Pluronic F-127-poly ( $\epsilon$ -caprolactone) nanofiber mats also enhance the function of the scaffold. The distribution of antimicrobial agents through a scaffold helps in the killing mechanism and results in synergistic efficacy against the biofilms. This approach had an important promise for treating infections associated with biofilm formation, which are often challenging to eradicate the conventional therapies. The successful demonstration of the antimicrobial delivery on human skin highlights their potential on clinical application in treating the wounds infected with bacterial biofilms. The research and development in this area could lead to the development of novel therapies for combating antibiotic-resistant infections and improving patient outcomes(84).

The current invention of core-shell nanofibers incorporated with PEO, chitosan (CS), PVP, and gelatin gains the progress in the study of dual drug delivery of vancomycin and Primaxin (imipenem/cilastatin)(85). These nanofibers, with an average diameter ranging from 218 to 342 nm, were used in diabetic foot ulcer infections, particularly in methicillin-resistant *Staphylococcus aureus* (MRSA). By incorporating the antibiotics into these nanofibers allowed a controlled release of drugs which target on bacterial strains like MRSA, *Escherichia coli* and *Pseudomonas aeruginosa*(86). The approach minimizes the risk which are associated with traditional drug delivery methods, such as nephrotoxicity and cytotoxicity(87). The work also focused on fabricating the electrospun nanofibers with anti-inflammatory and antipyretic properties. This research also highlights the importance for nanofiber-based therapies to address complex medical challenges while minimizing systemic side effects (71,88). Fig. 5. The comparative studies of polymers are summarized in the table 2.

The combination of copper sulfide with PVP and gelatin nanofibers gives several beneficial medical properties wherein, Copper sulfide was recognized for its antimicrobial properties that helps to kill microbes, while PVP and gelatin offer structural support and biocompatibility. PVP are often used in medical field for their ability to form films and fibers and making it an excellent substance for creating nanofibers. Gelatin obtained from collagen act as a biodegradable material



and were widely used in wound healing applications. By blending these materials into composite nanofibers, Liu et al. achieved a co-operative effect, where each and every compound contributes its unique properties and enhance the material's overall performance. This approach demonstrated the innovation and gained the importance for various biomedical applications, including wound dressings and antimicrobial coatings(89,90).



**Fig. 5.** Schematic representation of electrospun nanofiber-based wound healing systems with corrected chemical proportions.

**Table 2. Polymers in Wound Dressings: A Comparative Study of Material Properties and Performance Parameters**

S.No	Parameter	PCL	PVA	PEO
1	<b>Polymer Type</b>	Hydrophobic aliphatic polyester (91)	Hydrophilic water-soluble polymer	Hydrophilic non-ionic polymer
2	<b>Fabrication Methods</b>	Electrospinning, solvent casting, nanoparticles, core-shell fibers	Electrospinning, hydrogels, freeze-drying	Hydrophilic matrix/tablets, hydrogels
3	<b>Typical Siderophore Type Studied</b>	Few direct reports (inferred from drug/antibiotic models)	Few direct reports (hydrogel matrices) (92)	Not commonly reported for siderophores, used in controlled release



4	<b>Loading Efficiency/Mechanism</b>	Compatible with hydrophobic drugs or hydrophobic modifications of siderophores when encapsulated in particles (93,94)	Good entrapment with hydrophilic drugs; rapid release for water-soluble siderophores (94)	Facilitates diffusion-controlled release due to swelling/erosion (95)
5	<b>Release Profile</b>	Sustained, slow release over weeks/months due to hydrophobicity and crystallinity (96)	Burst or rapid release depending on gel/swelling; tunable via crosslinking	Fast release with hydrophilic swelling; slower with high MW grades
6	<b>Mechanical/Physical Properties</b>	Good mechanical strength; slow biodegradation suitable for implants (97)	Flexible hydrogel; water solubility can limit mechanical integrity unless crosslinked	High water uptake; matrix can erode rapidly, weaker mechanical strength
7	<b>Advantages for Siderophore Delivery</b>	Sustained release ideal for prolonged antimicrobial action; strong network for protective encapsulation (98)	High loading for hydrophilic siderophores; tunable porosity & swelling (6)	Enhanced diffusivity; rapid release useful for acute siderophore payloads (99)
8	<b>Limitations</b>	Hydrophobicity may impede loading of hydrophilic siderophores; slow degradation	Rapid initial release (“burst”) may limit duration; water solubility may lead to fast clearance	Rapid erosion/swelling may undermine controlled, long-term delivery
9	<b>Best Use Cases</b>	Long-term localized delivery (e.g., implanted coatings, nanofiber mats)	Hydrogel pads/films for wound or topical delivery	Oral/implant hydrophilic matrix where rapid release is acceptable

All these innovations and studies related to nanofibers paved the way for a solution of biofilm formation. Electrospun nanofibers can mimic the architecture of natural extracellular



matrices, making them suitable for medical applications. These nanofibers give a good environment for cell adhesion, proliferation, and differentiation (97,100). They are used in the regeneration of various tissues and organs, including skin, bone, cartilage, nerve, and blood vessels (53,101). Electrospun nanofibers also serve as carriers for controlled and targeted drug delivery. Researchers attained sustained release profiles, improved drug stability, and enhanced therapeutic efficacy by incorporating drugs, growth factors, or other bioactive molecules into the polymer matrix during electrospinning. Studies also proved that electrospun nanofibers-based drug delivery systems are effective for applications in cancer therapy, wound healing, and treatment of infections (102–104). The schematic representation are illustrated in Fig.

## 11. Conclusion

Electrospun microbial siderophore-based nanofibers represents as an innovative strategy to witness the challenges faced in biofilm-associated chronic wounds. By using this iron sequestration to disrupt microbial metabolism, quorum sensing, and biofilm maturation, these nano-engineered dressings offer the advantage over a traditional antimicrobial, including reduced risk of resistance development and multifunctional wound support. The ability of electrospinning to generate nanofibrous matrices with tunable architecture, high surface area, and controlled release profiles further strengthens the potential of siderophore-loaded systems as advanced wound care platforms that simultaneously promote antimicrobial activity, modulate inflammation, facilitate granulation tissue formation, and support cell adhesion and proliferation. Despite these promising attributes, the translation of siderophore-based nanofibers from bench to bedside are controlled by several challenges. The current studies are limited to *in vitro* or short-term *in vivo* models due to inefficiency of long-term biocompatibility, immunogenicity, iron homeostasis disruption and host–microbiome interactions. The variability in siderophore source, stability under physiological wound conditions and controlled release kinetics within complex wound environments require optimization. Regulatory and clinical considerations further complicate translation, as siderophore-based dressings may be classified as combination products, necessitating rigorous safety, toxicity, and efficacy evaluations. Future research should therefore prioritize standardized *in vivo* wound models, long-term safety assessments, and comparative studies against existing clinical dressings. Integrating smart or stimuli-responsive nanofiber



systems, synergistic combinations with growth factors or probiotics, and advanced delivery strategies may further enhance therapeutic outcomes.

To conclude, the microbial siderophore-based electrospun nanofibers holds a substantial promise as next-generation “nanohealers” for biofilm-infected chronic wounds and their clinical realization will depend on interdisciplinary efforts that bridge materials science, microbiology, pharmacology, and regulatory science. Addressing these translational gaps, it would be essential to harness their therapeutic potential and to advance these systems toward safe, effective, and clinically viable wound care solutions.

### **Data Availability**

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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### **Ethical approval**

Ethical approval was not applicable for this study.

### **Clinical Trial Number**

Not Applicable.

### **Declarations Conflict of interest**

The authors declared no conflict of interest.

### **Author Contributions**

Sitalakshmi Thyagarajan & Senthamil Selvi Poongavanam contributed to the conception, literature review, manuscript preparation, and final approval of the article and acted as the corresponding author.

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## Data Availability Statement

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The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

