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Review of Possible Applications of Nanofibrous Mats for Wound Dressings

Pregled načinov uporabe nanovlaknastih kopren pri oblogah za rane

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Abstract

Skin is an important part of the human body. Its function is to control the body's homeostasis mechanism. If a skin injury occurs, it is of utmost importance to heal the skin as soon as possible. The currently available medical treatment system, however, has limited effectiveness on the regeneration of the structure and function of the injured skin, potentially causing wound infections and dehydration. The corresponding impact on the healing process may in the worst case also be fatal. To overcome these problems in wound dressing materials, nanofibrous mats are excellent candidates for wound treatment and management. Such wound dressings can be found in biomedical applications not only in drug delivery, but also as antibacterial and antimicrobial materials, and as materials for the regeneration and repair of tissue or organs. The large surface-area-to-volume ratio is one of the unique properties of nanofibrous mats. This paper gives a brief overview of possible materials and applications of nanofibrous mats for wound dressing.
Keywords: wound dressing, electrospinning, drug delivery, nanofibrous mats

Izvleček

Koža je pomemben del človeškega telesa. Njena naloga je nadziranje mehanizma homeostaze človeškega organizma. Če se koža poškoduje, je zelo pomembno, da jo čim prej zdravimo. Obstoječi sistem zdravljenja ne zagotavlja učinkovite obnove strukture in funkcije poškodovane kože, kar lahko vodi v okužbe ran in dehidracije, ki je lahko v najslabšem primeru tudi usodna. Za odpravo omenjenih težav pri sodobnih oblogah za rane so nanovlaknaste koprene odlična možnost za zdravljenje in oskrbo ran. Takšne nanovlaknaste koprene se lahko uporabljajo tudi v biomedicinske namene, ne le kot transdermalni obliži, temveč tudi kot protibakterijska in protimikrobna sredstva ter kot materiali za regeneracijo in obnovo tkiv ali organov. Ena od edinstvenih lastnosti nanovlaknastih kopren je njihovo veliko razmerje med površino in prostornino. V članku je podan kratek pregled materialov in možnosti uporabe nanovlaknastih kopren pri oblogah za rane.
Ključne besede: gaza, elektropredenje, doziranje zdravil, nanovlaknaste koprene

1 Introduction

The normal time for the wound healing process is about 2–3 days to some months, depending on the depth of the wound and the chronic condition. The healing of chronic wounds can take from a few months to several years. The classic wound dressing often has a poor fit; it is stiff and relatively hard, whereas wound dressings from nanofibrous mats are extremely thin and flexible. This type of nanofibrous mats has a breathable and water-absorbing effect, and can perfectly adapt to the wound geometry due to its high flexibility and soft surface wound dressing.
The process of modern drug delivery faces challenges, e.g. low solubility, bioavailability or targeted delivery of drugs with limited duration. Electrospun

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nanofibrous mats can overcome these problems [1, 2]. Their high surface-to-volume ratio enables improved interactions with the environment, making them promising for wound care, drug delivery and biotechnology applications. Nanofibres can thus be used for biomedical applications such as tissue engineering, wound healing processes and targeted drug delivery systems [3–9].

According to the results of several research groups, nanofibrous mats have the ability to absorb large concentrations of wound exudates without causing infections, and release anti-microbial and anti-inflammatory agents. Nanofibrous mats have been shown to be ideal candidates for modern and efficient wound treatment, and wound care. Being produced effectively and inexpensively in an electrospinning process, they offer a multi-promising strategy for modern wound treatment [10–13].

Nanofibres can be electrospun from natural or synthetic polymers such as polysaccharides, collagen, keratin, silk, tubulin, actin, cellulose, polyacrylonitrile (PAN), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), acrylonitrile butadiene styrene (ABS), poly(lactic-co-glycolic acid) (PLGA), polyurethane (PU), polyvinyl alcohol (PVA), polycaprolactone (PCL), polymethyl methacraylate (PMMA), chitosan, fibrin, poly(ethylene glycol) (PEG), gelatine, casein and alginate. These and many other polymers are known in tissue engineering and are applicable in wound dressing [14–25].

2 Electrospinning techniques

Electrospinning is a technology which can be used to produce continuous ultrathin nanoscale fibres or fibre mats composed of fibres with the diameters in nanometre range [26–31]. Ultrathin fibres can be produced easily using this technology from multitude of materials, e.g. polymers, polymer composites, inorganic [32] or inorganic/organic [33] materials, or even ceramics [34]. These types of nanofibres are especially useful in the applications which necessitate large surface areas, such as promotion of cell growth in biomedical applications, catalysers, novel filter materials, medical wound dressings etc. [35–37].

Electrospinning processes can be performed in two slightly different ways, i.e. using needle-based or needleless electrospinning techniques (Figure 1). Electrospinning with a needle is a simple process which depends on a high voltage power supply with adjustable control, a polymer solution reservoir (e.g. a syringe with a small diameter needle) with or without a control pump and a metal collecting screen. The spinnable polymeric solution is put into a reservoir with a metal needle or tip and connected to a power supply, enabling the formation of a charged polymer jet. The conductive collecting screen the nanofibres are deposited on can either be a stationary plate or a rotating platform or substrate. The plate can be used to manufacture non-woven nanofibrous mats, while the rotating platform can be used to prepare both randomly oriented and aligned fibres. With a vertical and a horizontal orientation, two standard electrospinning setups are available. Three essential operating parameters play a decisive

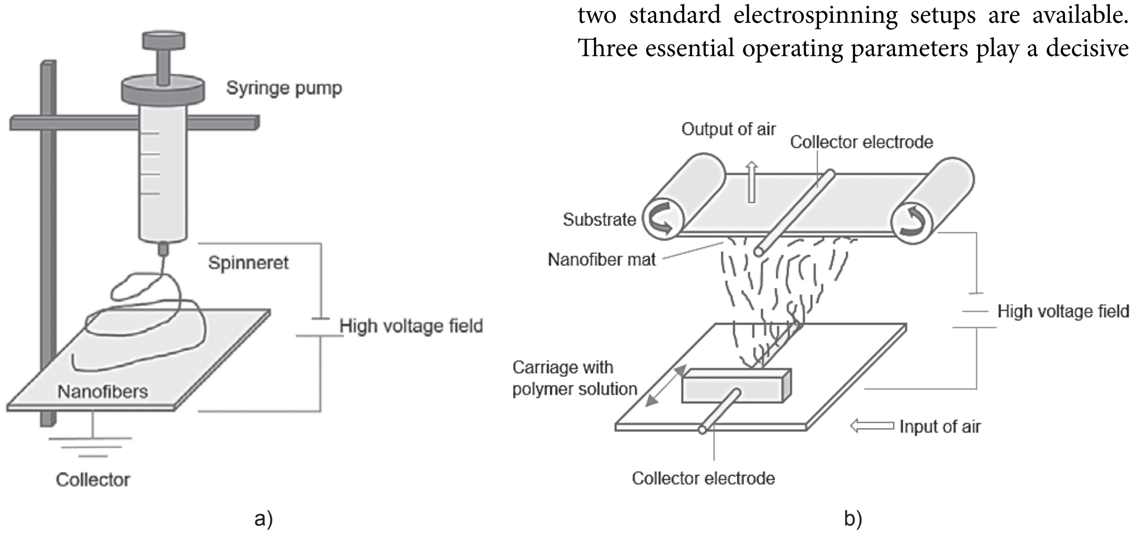


Figure 1: Basic set-up for (a) needle based and (b) needleless (Nanospider) electrospinning

role: namely the solution parameters, process parameters and environmental parameters [38, 39].

Needleless electrospinning is a technical process that allows electrospinning of nanofibres directly from an open liquid surface in a self-organized way. The fibre quality and productivity of spinnerets play the most important roles in needleless electrospinning. These spinnerets are connected with a high voltage power supply and a dosing unit for the spinning solution. Spinnerets for needleless electrospinning can be divided into two types, i.e. rotating or stationary spinnerets according to the working states. The rotating spinnerets can transfer mechanical vibration to the polymer solution, which results in establishing jets, mostly working continuously. An auxiliary force (e.g. a magnetic field, gravity or gas bubbles) is mostly used to establish a stationary spinneret in the electrospinning process.

Separated solution containers are used for the spinning solutions for roller and cone electrospinning. The whole process can be described by the following four steps: first, a thin layer of a polymer solution is set up on the spinneret surface which is immersed in the solution and rotated, and then, the rotation helps to create conical spikes on the solution surface. After that, by applying high voltage, the spikes concentrate the electric forces to create Taylor cones. Finally, jets spread out of the Taylor cones and produce fibres [40–42].

Especially "green" electrospinning, which avoids dangerous solvents, is of high interest in research nowadays. To prepare such nanofibrous mats, different (bio-)polymers can be electrospun from aqueous or other non-toxic solutions.

3 Electrospinnable polymer materials for wound dressing applications

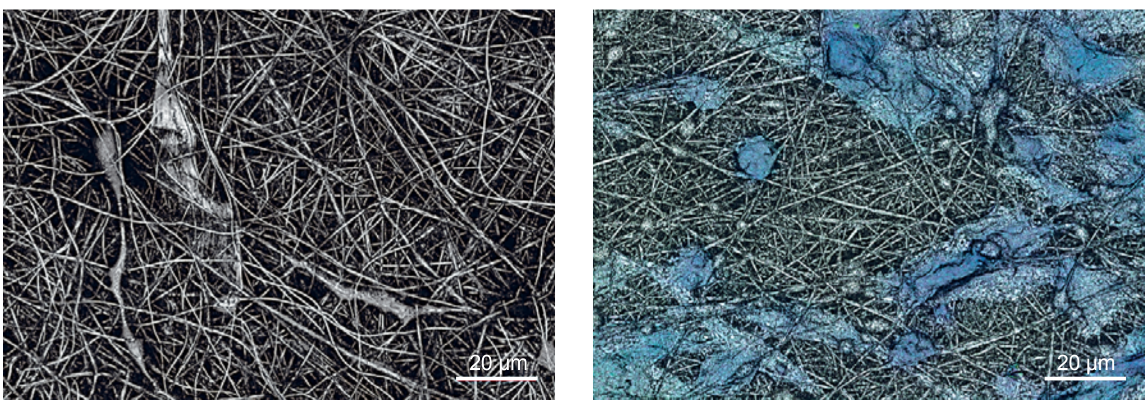
Frequently used polymers which are spinnable from non-toxic or low-toxic solvents are, for example, polyacrylonitrile (PAN, spinnable from dimethyl sulfoxide, DMSO) and poly(ethylene glycol) (PEG, spinnable from water) [43–45]. PEO and PVA are often used as the spinning agent for materials which cannot form fibres solely [46].

There are some other water-soluble polymers which have additionally interesting specific properties. Poloxamers (poly(oxyethylene-b-oxypropylene-b-oxyethylene)) can be used in blends with other polymers for drug delivery, skin tissue engineering or wound healing [47].

Dextran (carbohydrate gum formed by the fermentation of sugars and consisting of polymers of glucose) can be used for drug delivery in wound dressings or electrochemical applications in different types of blends [48]. PAN, on the other hand, is often applied for electrospinning as a precursor to produce carbon nanofibrous mats [49, 50].

Blends of different polymers are often used to produce multi-material nanofibrous mats [51] with new properties. Blending PAN with cellulose acetate can be used to increase the absorption properties of activated carbon nanofibres [52]. PAN/gelatine blends can be used for the promotion of cell growth (Figure 2) [53–55].

In bio-medicine and bio-technology, chitosan and sodium alginate have good biocompatible and



a) b)

Figure 2: Confocal laser scanning microscope (CLSM) images of (a) PAN/gelatine nanofibrous mat and (b) CHO-DP12 (Chinese hamster ovary) cells on PAN/gelatine nanofibrous mat, coloured with methylene blue on scale bar indicates 20 µm

non-toxic features, and are both widely applicable in the medical sector [56–59]. Moreover, chitosan/polyaniline composite nanofibrous mats have shown anti-bacterial properties and were found to be capable of accelerating wound healing processes [60].

PEO blended with alginate was used to prepare scaffolds by electrospinning to support human dermal fibroblast cell attachment. Nanofibre scaffolds were found to promote tissue cell adhesion and enable encapsulation of drugs [61, 62].

Chronic wound care products were improved using chitosan (PEO)/silica [73] and polyvinyl alcohol (PVA) blended with chitosan. Similarly, PVA/chitosan nanofibres, as well as collagen/PEO wound dressings were shown to have high moisture vapour transmission characteristics, good antimicrobial function and no cytotoxic effects [64–66].

Generally, nanofibrous mats can serve as a base for therapeutic agents or can accelerate chronic wound healing processes [67, 68]. A new generation of wound dressing can also be produced by electrospinning materials with high moisture absorption and anti-bacterial effects, including elements like zinc or copper alginate. These types of wound dressings contain bioactive elements, such as antimicrobial, anti-bacterial and anti-inflammatory agents, which can be released to wounds to improve their healing process [69]. Alternatively, it is even possible to electrospin fibres including commensal bacteria for medical purposes [70].

PVA/BS nanofibres have shown large potential for drug delivery, tissue engineering and tissue repair substitute properties in wound dressing [71]. PU/chitosan has been examined as well, showing promising features for wound dressing applications similar to many other biopolymer blends, e.g. blends with starch or silk [72–75].

One of the most sufficient biodegradable substances in nature is cellulose, which is widely applicable in the electrospun nanofibrous mats production [76–78]. It can be produced from certain bacterial species by fermentation. However, it is traditionally extracted from plants. Bacterial cellulose (BC) is extracted mainly from microorganisms belonging to the genera *Gluconacetobacter*. BC is widely used in biomedical applications, e.g. in drug delivery and tissue engineering [79]. It can be used to decrease pain and accelerate granulation, supporting a perfect wound healing process. It is also useful in the creation of a moist environment at the wound area and absorption of exudates. Furthermore, it can prevent microbial infections [80].

Bacterial cellulose-alginate nanocomposites were successfully produced by nanotechnology and they showed excellent antibacterial activity [81, 82]. The synthesis of BC/chitosan or chitosan/gelatine composites with high mechanical reliability and antibacterial activity was investigated by different research groups [83–87]. Similarly, chitosan blended with metallic nanoparticles has an effect on the microbial activity and wound healing [98].

The reductions of inflammatory cells and mostly closed capillary lumens have been investigated by diverse research groups, using silver nanoparticles in diverse polymer matrices [89–97].

Another investigation showed strong antibacterial and anti-inflammatory characteristics of silver nanoparticles [98]. Co-electrospinning of polyurethane and keratin which can be extracted, e.g. from human hair and fixed with silver nanoparticles, results in PU/keratin/Ag composite mats of nanofibres. These nanofibrous mats showed very good cell viability and antibacterial properties, and were thus able to promote wound healing [99]. Similarly, PU or nylon nanofibres with silver nanoparticles showed excellent antimicrobial properties [100].

Polyurethane-cellulose acetate-zein composite nanofibrous mats were found suitable for drug delivery and to have good antibacterial bio-active wound recovery characteristics [101].

Polylactic acid (PLA) nanofibres with Fe_3O_4-COOH have strong antibacterial and drug delivery activities for wound dressings and other biomedical applications [102]. PLA/CNC/PEG composite nanofibres showed therapeutic drug release properties and allowed for controlling long-time drug delivery in wound dressings [103]. Spirulina extract-alginate PCL and PCL-gelatine nanofibres were also found to show excellent wound care properties, especially for tissue regeneration [104–106].

Collagen is a widely used natural polymer substance for biomedical applications [107, 108]. It has gained broad clinical and consumer adoption as a secure material. To architecturally imitate the skin structure, nonwoven nanofibrous mats from collagen can be applied in wound healing processes which are typically produced by electrospinning. As a major fibrous protein in the extracellular matrix (ECM), collagen plays an important role in maintaining the biological and structural integrity of ECM [109, 110].

For the cell attachment, proliferation and differentiation, nonwoven collagen nanofibrous mats are of utmost importance. Moreover, these collagen nanofibrous mats are designed to induce platelet adhesion and aggregation to increase the congealing, which is favourable in wound dressing applications for the improvement of cell adhesion and proliferation [111].
Carboxymethylcellulose (CMC)/dextran hydrogels were activated with a gallium bio-glass and can be applied to reduce cancer cell viability particularly for high Ga contents in the bio-glass. CMC hydro gels cross-linked with oxidized dextran or alginate/CMC were found to significantly support the wound healing and skin regeneration [112].

4 Conclusion

A remarkable improvement has been gained in the development of therapeutic approaches to be used in the treatment of chronic wounds. Among the developed types of wound dressings, electrospun nanofibres are taken into consideration as one of the most effective wound dressing materials for the near future. They show a high surface area to volume ratio as well as a porous structure that improves homeostasis, prevents infections, absorbs exudates, enables gas permeability and cell adhesion, migration, proliferation and properly targeted drug delivery.
Several functionalization methods can be used to improve the surface properties of nanofibres or to produce nanofibres for carrier-based drug delivery, e.g. with blending electrospinnable polymers with diverse nanoparticles. Combining the intrinsic properties of diverse (bio)polymers with additional functions added in this way, electrospun nanofibrous mats belong to the most promising candidates for improved wound management.

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