ORIGINAL PAPER

Polyvinyl Alcohol (PVA)–*Azadirachta indica* (Neem) Nanofibrous Mat for Biomedical Application: Formation and Characterization
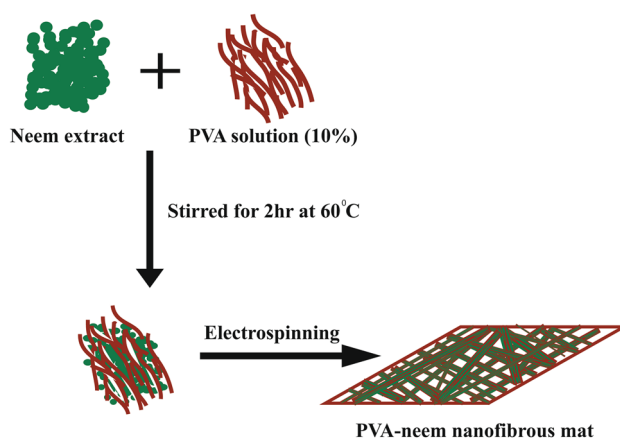
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Abstract

The present study provides credence to the formation of polyvinyl alcohol (PVA)–*Azadirachta indica* (neem) nanofibrous mat (PNNM) under optimum processing conditions of electrospinning technique from a mixer of PVA and neem extract to utilize the inherent medicinal properties of this herb for biomedical application. The bonding behavior, orientation of fibers, thermal behavior, and moisture management properties were evaluated by Fourier transforms infrared spectroscopy (FTIR), scanning electron microscopy (SEM), thermo gravimetric analysis (TGA) and moisture management tester (MMT) reports respectively. The antibacterial activity of the developed sample at the maximum mixing ratio of neem extract (80%) was tested against Gram-positive (*S. aureus*) bacteria using agar disc diffusion method. The results reveal that the prepared nanofibrous mat exhibited better thermal and moisture management properties in comparison with PVA nanofiber alone. The formation of smooth fibers was confirmed by SEM images having average diameter of 185 nm under 5k, 10k and 15k magnifications. The characteristic peaks of PVA and neem constituents in FTIR spectra of the developed mat confirmed the presence of both components. Bacterial resistance was reached up to 20 mm due to the antibacterial constituents of neem extract. Thus the developed mat could be used as a biocompatible and bio based in biomedical applications.

Graphic Abstract

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Introduction

The growing public awareness about the effects of nanoparticles (including nanosized antimicrobial agents i.e. silver) and synthetic antibiotics on the environment, human health, and/or bacteria resistance issues has triggered a surge

in the use of natural antimicrobial compounds because they are expected to be nontoxic, environmentally sustainable, and less prone to create resistant bacteria. Because of its improved biocompatibility, biodegradability, low toxicity, and intrinsically large surface area; nanofibrous mat produced from the natural polymers with biological activities have recently emerged as novel mat materials for biomedical applications, such as wound dressing, tissue engineering, and drug delivery [1]. Hence, there is a renewed interest in both academic and industrial sectors about antimicrobial nanofibers which represent a particular area that combines the intrinsic properties of the nanofibers with biocidal action. Although these polymeric nanofibers can be produced by a number of techniques including drawing, template synthesis, phase separation and self-assembly, among others, electrospinning turns out to be most frequently used electrofluidodynamic technique (EFDT) due to its high versatility and unique capability to generate fibers ranging from several micrometers to nanometers under applied electrical forces in addition to its cost-effectiveness, production of continuous nanofibers and easiness for industrial application [1–3]. This technique being simple and incredibly straightforward can also be applied to different polymers [4–7]. The basic electrospinning setup consists of four components: a syringe loaded with a polymeric solution, a metal needle, a power supply working at kV range and a metallic collector. The process involves the interaction of the polymer solution moving at a constant flow rate with a high-voltage electric field at the tip of the needle is directly connected to a power supply.

Owing to the large surface-to-volume ratio that offers a highly active contact surface to electrospun nanofibrous mat having the porous structure favors cell adhesion, proliferation, and differentiation [1, 3, 8–11]. Besides, it attains a uniform adherence to wet wound surface without any fluid accumulation and thereby can meet the key requirements of the higher gas permeation and the protection of the wound from infection and dehydration [12]. Therefore, electrospun nanofibrous mats containing a natural remedial plant extract hold a promise to be used for various biomedical applications especially for wound dressings due to the inherent medicinal properties of the plant extracts [13–16]. For instance, nanofibers from polyacrylonitrile-moringa extract were fabricated and characterized for antimicrobial and wound healing applications [17]. Besides, nanofibrous mats from the mixer of PVA-aloevera, PVA-henna, PEO-henna, polycarbonate/leaf extract, and PCL-natural extract were also investigated by numerous studies [4, 18–20]. Without this, composite nanofibers from recycled poly (ethylene terephthalate)/polyacrylonitrile/styrene by electrosping [21], Chitin nanofiber-reinforced xanthan gum hydrogels [22], fabrication of chitosan/nylon 6 and tannin/nylon 6 nanofiber for effective adsorption of Cr(VI) [23],

porous composite nanofibers from the mixer of polyacrylonitrile/polyvinylidene fluoride nanofibers by inexpensive salt using for dye adsorption [24], electrospun polymer nanofiber adsorbent material for metal ion removal [25], development of CS/PVA biodegradable composite nanofibers through electrospinning as a microporous material with well controllable procedure [26], nanofiber composite materials cationic/anionic chitin [27], ZnO nanoparticles doped core–sheath nanofibers by electrospinning with antimicrobial properties [28] are some mentionable recent studies conducted by several researchers towards the diverse application of electrospun nanofibers fabricated from the mixer of different polymers.

The name *Azadirachta indica* prominently known as neem, is one of the commonly used medicinal plants, containing Azadirachtin as the main active ingredient, is widely used in the Indian subcontinent due to its large range of biological activities including antiulcer, antibacterial, anti-inflammatory, antimalarial, antifungal, antiviral, antioxidant, antimutagenic and anticarcinogenic [29, 30]. It contains more than 140 active substances which are broadly classified as isoprenoids and nonisoprenoids and have been used traditionally for the treatment of inflammation, infections, fever, skin diseases and dental disorders [31–33]. Although all parts of a neem tree have bioactive compounds, the leaf of neem is a virtual 'storehouse' of organic compounds and the principal constituents of neem leaves are carbohydrate, crude protein, crude fiber, fat, ash, amino acids and minerals [2, 32]. Besides, the leaves also possess phytochemical constituents such as- 3-Acetyl-7-tigloyl-lactone-vilasinin, 3-Desacetyl-3 cinnamoyl-azadirachtin, 3-Desacetyl-salanin, 4a, 6a-dihydroxy-A-homo-azadiradione, 6 desacetylnimbinene, azadirachtanin, azadirachtanin-A, aeta-sitosterol, hyperoside,isoazadirolide, nimbaflavone, nimbandiol, nimbinene, nimbolide, quercetin, quercitrin, rutin and vilasanin [30]. The presence of different bioactives like assteroids, sugars, triterpinoids, alkaloids, reducing sugars, tannins, flavonoids, sesquiterpene lactones, and phenolic compounds [34, 35] are mainly responsible for the antibacterial properties of this plant [36–40]. Conventional extraction methods (methanolic, acetonic, and aqueous) of neem leaves inhibit the growth of *Escherichia coli*, *Micrococcusluteus*, *Enterobacter*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Klebsiellapneumoniae*, *Streptcoccuspyogens*, and *Staphylococcus aureus* when studied using agar diffusion methods [29, 35, 41–44]. All the properties of this wonder plant collectively have made it a potential candidate to be used for antibacterial and wound healing purposes [45–47]. However, the natural form of this herb offers limited acceptability in wound healing process which has been overcome by utilizing new approaches including electrospinning, electrospraying, solution blow

spinning and film casting to use plant extracts in the form of suitable products to serve as wound dressing materials [14, 48]. Although, the formation of nanomat from corn and neem oil [49] and propolis oil/neem oil [50] and neem oil [51] for bone engineering, tissue engineering and blood compatibility respectively where PU was used as a carrier polymer but the solvent used in all previous studies is DMF which was removed before testing the developed mat. Albeit, DMF was removed but this substance is usually cause the skin and lever problems; recent evidence shows that liver damage may occur in exposed workers who appear to be healthy. DMF is also known to cause skin problems and alcohol intolerance [52–55] which restrict its use for wound dressing purpose. The use of such solvent needs to be avoided considering the environmental impact because PVA is a non-hazardous, biocompatible, biodegradable and having good physical properties as a carrier polymer for electrospining and wound dressing purpose as well. Without this, the contents of neem should be increased in the spinning solution to reduce the amount of carrier polymer.

However, to the best of our knowledge, the development of a nanofibrous mat from PVA polymer mixed with neem leaves extract has not yet been reported. Thus, the objective of this study is to form and characterize the nanofibrous mat from a mixer of PVA and neem extract using electrospinning technique for its use in the biomedical field especially wound dressing purpose.

Materials and Methods

Materials

The leaves of *Azadirachta indica* were collected from the local area of Gazipur city, Dhaka, Bangladesh. Polyvinyl alcohol (PVA) with molecular weight (MW) of 1, 15,000, DP of 1700–1800, viscosity: 26–32 cps, 99% hydrolyzed granules was sourced from Loba Chemical (India) and absolute ethanol with the purity of 99% was purchased from Merck, Germany. All the chemicals were of analytical grade and used without further purification.

Preparation of Neem Extract

First of all, the collected leaves being washed repeatedly with fresh water were oven-dried at 45 °C. Then the dried leaves were finely ground to powder form and stored in airtight containers. Ten gram of the powder was taken in a flask containing 100 mL of ethanol. The flask was kept aside for 24 h at room temperature to ensure perfect maceration. Next,

the macerate was filtered through nylon mesh and directly used as neem extract by mixing with PVA solution.

Preparation of PVA-Neem Solution

The prepared PVA solution was kept in clean glassware where the neem extract with different concentrations i.e. 20%, 40%, 60%, and 80% were added separately. Water was used as solvent for PVA. A magnetic stirrer was used to make solution uniform and homogenous for 1 h under warming condition because at room temperature PVA molecules tend to aggregate and become separated from neem extract. The prepared solution is then transferred via a syringe (30 mL) to the pump. Samples identity with the solution ratio is shown in Table 1.

Characterization

Morphological Observation

The morphological orientation of nanofibers in the samples was observed by scanning electron microscopy (SEM) (SU 1510, Hitachi, Japan) at a magnification of ×3000 and ×5000 with a voltage of 2 kV and 5 kV respectively to achieve actual images.

Thermal Properties

Thermal behavior i.e. thermo gravimetric analysis (TGA) of the developed mats was evaluated by a thermal analyzer (SDT 650, Discovery, USA) at the temperature range of 60–300 °C with a constant heating rate of 5 °C per minute. Approximately 8 mg samples were taken as sample and subjected to heat to evaluate its characteristics.

Measurement of Moisture Management

Moisture management property of the developed mat was evaluated by a moisture management tester (MMT) (model: M290, SDL Atlas, UK) according to the method of AATCC 195–2009. Wetting time, absorption rate, maximum wetted radius and spreading speed of inner and outer surface including accumulative one-way transport capacity (R) and overall

Table 1 Samples identity with solution ratio

Samples identity	PVA (10%)	Neem extract (%)
N1	20	80
N2	40	60
N3	60	40
N4	80	20

moisture management capacity (OMMC) was measured following the above-mentioned standard to categorize the mat based on its interaction with liquid. All the readings were taken multiple times to take average value.

Antibacterial Assay

The antibacterial activity of the electrospun nanofibrous mat was studied using disc diffusion method against *Staphylococcus aureus* (*S. aureus*) and the zone of inhibition was measured due to the prominent influence of *S. aureus* towards wound infections on the skin. A qualitative disk diffusion test using 10^2 colony forming units (CFUs) of the *S. aureus* being cultured on Nutrient Broth (NB) agar plates was done. Then, a single colony was transferred via a loop to a tube containing 9 mL of TSB and a homogenous mixture was made using a shaker. Next inoculated broth was incubated in a shaker incubator at 45 °C for 2 h to match 0.5 MacFarland standards. Then a sterile cotton swab was dipped into the broth culture and streaked evenly on MHA plates repeatedly. After 30 min, the sample along with positive control of amoxicillin antibiotic discs being transferred directly onto the sensitivity plates with the aid of sterile forceps and the plates incubated at 37 °C for 24 h. Finally, the zone of inhibition was measured. Each sample for the study was incubated by pelletizing the nanofibrous mat of a 7 mm diameter disc.

Fourier Transforms Infrared Spectroscopy (FTIR)

The chemical nature of PVA nanofibrous mats with and without neem extract was characterized using an FTIR (IRPrestige21, Shimadzu Corporation, Japan). The spectra of the samples were recorded in 400–4000 cm^{-1} range with 4 cm^{-1} resolution.

Statistical Analysis

All the results of quantitative measurement have been analyzed with mean and standard deviation in order for accurate measurement. The test results of different test have been taken as average value.

Results and Discussion

Parameters Optimization and Morphological Observation

Table 2 shows the optimum electrospinning conditions that were established in this study by trial and error method. No fiber is formed when the applied voltage is less than 12 kV because it cannot overcome the surface tension value of the solution which restricts the solution to flow towards the collector. Hence, a higher than 12 kV voltage difference was maintained for all samples. Because of the highest viscosity corresponding to a high mixing ratio of PVA, high pressure was required for sample N3 and N4.On the other hand, low pressure was maintained for N1 and N2 because of the addition of neem extract which reduces the viscosity of the final solution. However, a constant collector distance was maintained which is 15 cm for all samples. The SEM images of the developed samples have been shown in Fig. 1 which reflects the formation of nanofiber for all samples having an average diameter of 173.33 ± 27.95 nm under the magnifications of 5k, 10k and 15k respectively.

TGA Analysis

The thermal behavior of PVA-neem nanomat, in the form of TGA curve is shown in Fig. 2. The TG curve shows a linear degradation behavior with the initiation of degradation above 240 °C. Although the melting point of PVA nanofiber is 190 °C or 227 °C due to its higher amorphous region [56–58], the addition of neem extract shows enhanced initial degradation at a higher temperature of 240 °C. The PVA nanomat starts to melts at a temperature of 212 °C as shown in Figure whereas the PNNM starts to melt at 240 °C. This shows that the blend of PVA-neem is much more stable to thermal decomposition compared with the individual polymers. The increase in the melting point is due to the interactions of neem with PVA which retard the mobility of polymer chains, and consequently a higher energy is required to move the polymer chains in the nanomat. Up to 240 °C, the developed mat shows thermal stability despite there was some weight loss due to moisture removal but no polymer degradation result.

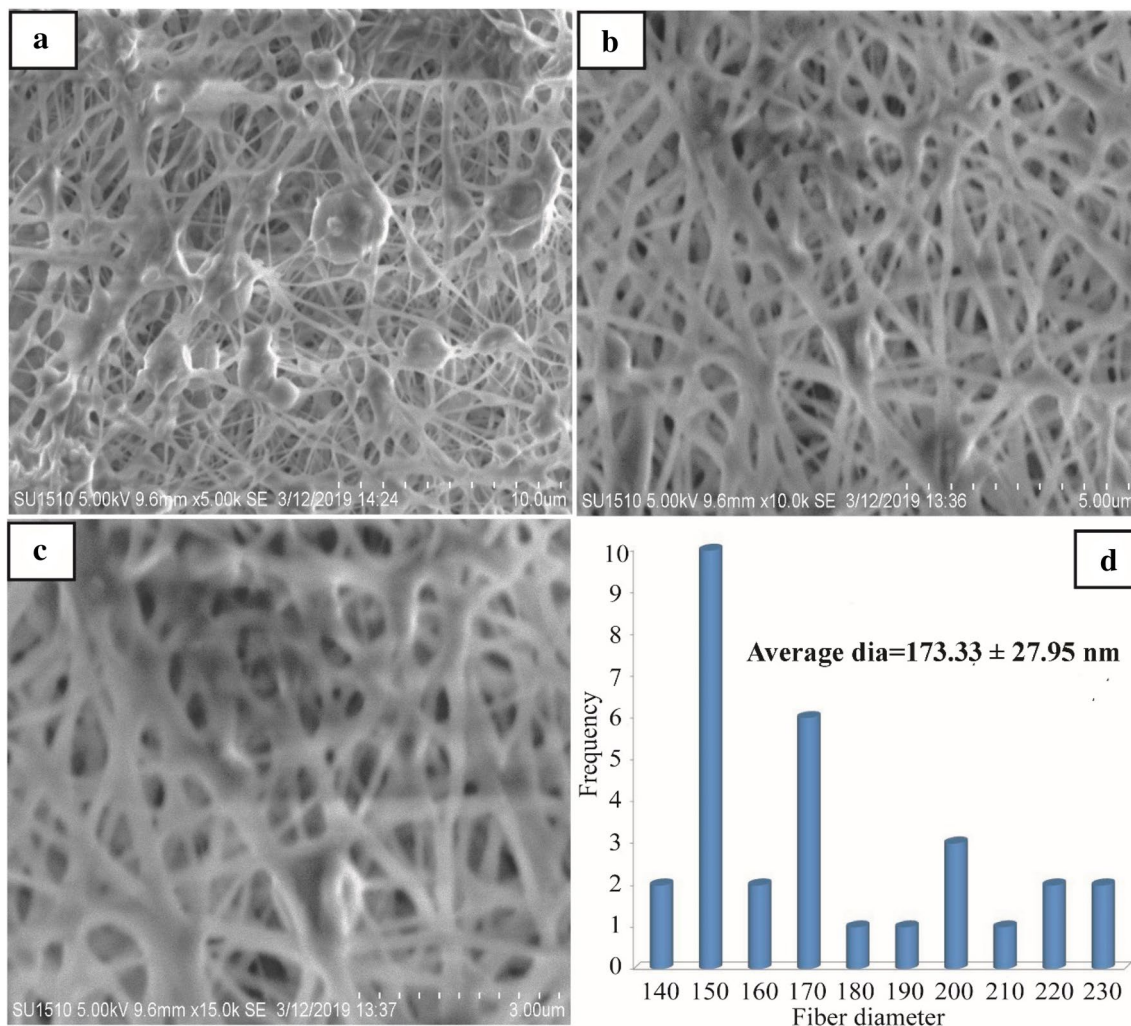| Table 2 Spinning conditions for different samples	Sample identity	Pressure (mL/h)	Positive (kV)	Negative (kV)	Collector (cm)	Heater (kV)
	N1	3.5	20	12	15	0.442
	N2	3.5	20	12	15	0.442
	N3	4.0	20	12	15	0.402
	N4	4.0	20	12	15	0.441

Fig. 1 SEM images of PVA-neem nanofibrous mats at 5 k (**a**), 10 k (**b**), 15 k (**c**) and distribution of fiber diameter (**d**) respectively for N4

Fig. 2 Effect of temperature on weight loss of PNNM and PVA nano-mat

Moisture Management Properties

In addition to having a biological action, the nanofibrous mat must also offer a high comfort at the dermal level of human skin. Hence, it is necessary to evaluate the capacity of transfer liquids (water or perspiration) from the skin to the external environment. The results of moisture management properties of the samples produced from PVA polymer and the mixer of PVA-neem have been shown in Fig. 3 and Table 3 respectively. The wetting time of top and bottom surface of PVA nanofibrous mat lies in the range of 3–5 s indicating its fast wetting nature whereas the value of N1 and N2 are much higher for the same parameter. It may be due to the addition of neem extract to the PVA solution which restricts the wettability of the samples. But the values of N3 and N4 lie in between of PVA and N1 and N2 which indicates their moderate wettability. This may be because of a higher proportion of the PVA solution in the mixer. Considering the
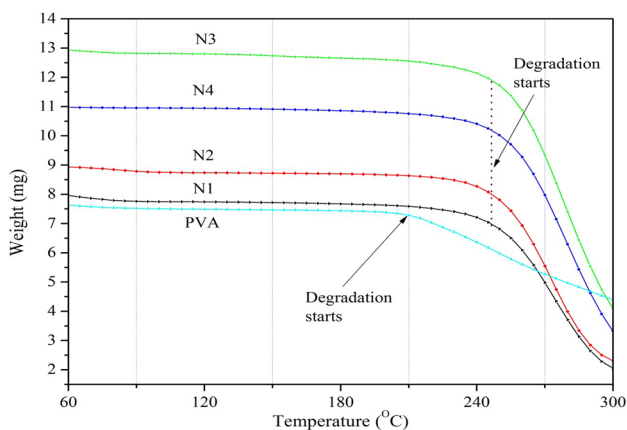
Fig. 3 Water location versus time diagram of the developed samples
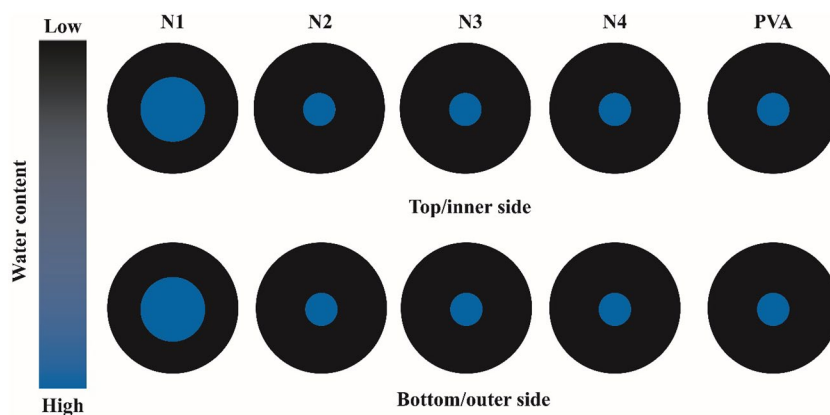

Table 3 Moisture management properties of PVA and PVA-neem nanofibrous mat

Samples identity	Wetting time (s)		Absorption rate (%/s)		Spreading speed (mm/s)		AOTI (%)	OMMC	Types as of AATCC
	Top	Bottom	Top	Bottom	Top	Bottom			
N1	5.5 (G-3)	5.6 (G-3)	230.2 (G-5)	37.1 (G-3)	1.10 (G-2)	1.1 (G-2)	54.5 (G-2)	0.2 (G-1)	Fast absorbing and slow drying
N2	5.2 (G-3)	5.2 (G-3)	299.5 (G-5)	103 (G-5)	0.90 (G-1)	0.9 (G-1)	901.7 (G-5)	0.7 (G-4)	Water penetration
N3	4.8 (G-4)	4.9 (G-4)	360.1 (G-5)	32.3 (G-3)	0.98 (G-1)	0.97 (G-1)	-275.3 (G-1)	0.1 (G-1)	Water repellent
N4	5.0 (G-4)	5.9 (G-4)	149.2 (G-5)	54.1 (G-4)	0.97 (G-1)	0.97 (G-1)	-230.0 (G-1)	0.12 (G-1)	Water repellent
PVA	3.5 (G-4)	4.6 (G-4)	34.8 (G-3)	22.7 (G-2)	1.33 (G-2)	1.04 (G-2)	-423.7 (G-1)	0.04 (G-1)	Water repellent

AOTI→accumulative one-way transport index, OMMC→overall moisture management properties, G→grade

G-1→poor, G-2→fair, G-3→good, G-4→very good and G-5→excellent

behavior of the absorption rate, all the samples excluding PVA show a better grading which suggests that the addition of neem extract to PVA solution enhances the absorption properties. This may be attributed to the adhesive nature of PVA polymer which inhibits the absorption capacity of the nanofiber. A maximum wetted radius was observed in the case of N1 (Table 3) which indicates that a higher proportion of neem extract in the electrospinning solution enhances the liquid spreading speed over the surface of the nanofibrous mat. Although the value of moisture spreading speed for the PVA nanofibrous mat is close to N1, this is limited to a lower wetted radius only which is 50% of the wetted radius of N1. However, the one-way transport capacity of N1 and N2 was observed maximum in comparison with PVA, N3, and N4 where the proportion of PVA is higher. This property along with overall moisture management capacity of N1 has made it a fast absorbing and slow drying fabric while N2 as a water penetration fabric but the nanofibrous mat produced from PVA, N3 and N4 can be considered as a water repellent fabric because of its poor one-way transport capacity as well as low overall moisture management capacity. So, it can be suggested that liquid/moisture can penetrate easily from one surface to another if the electrospinning solution is prepared by adding neem extract to the PVA solution.

Antibacterial Activity

The antibacterial activity of the nanofibrous mat plays the most crucial role in wound dressing purposes besides biocompatibility, thermal stability, and moisture management properties. Therefore, the antibacterial property of the prepared neem extract incorporating PVA nanofibrous mat against *S. aureus* is discussed in this section. Generally, the thicker cell wall of *S. aureus* makes it resistant to be destroyed by biocides (either natural or manmade). The antibacterial activity of the nanofibrous mat is presented in Fig. 4 showing the formation of an inhibition zone at a value of 20 mm. This may happen due to the ethanolic extraction process which may extract the antibacterial constituents from neem leaves. Again, the concentration of neem extract with PVA solution play an important role to form an inhibition zone, that's why sample developed with the maximum amount of extract has been tested. Besides, the mesho structures of the developed nanomat can prevent the penetration of any bacteria due to the presence of tiny pores and hence preclude the surrounding infections effectively [59]. Although the mechanism of killing bacteria by biocides like silver nanoparticles or chitosan has been well illustrated by researchers, further studies are needed to gain an

Fig. 4 Formation of zone of inhibition **a** PVA nanomat and **b** N1 against *S. aureus*
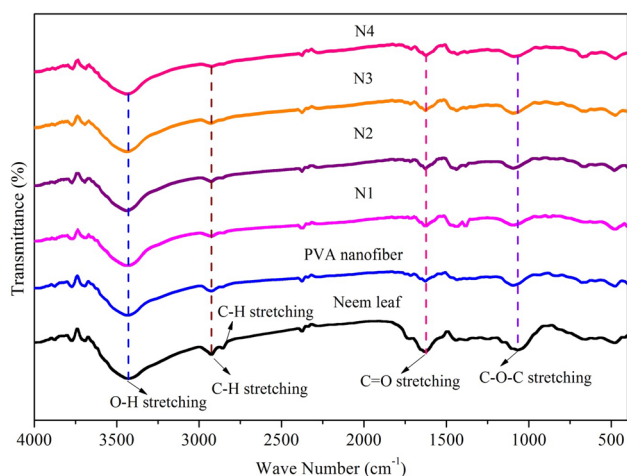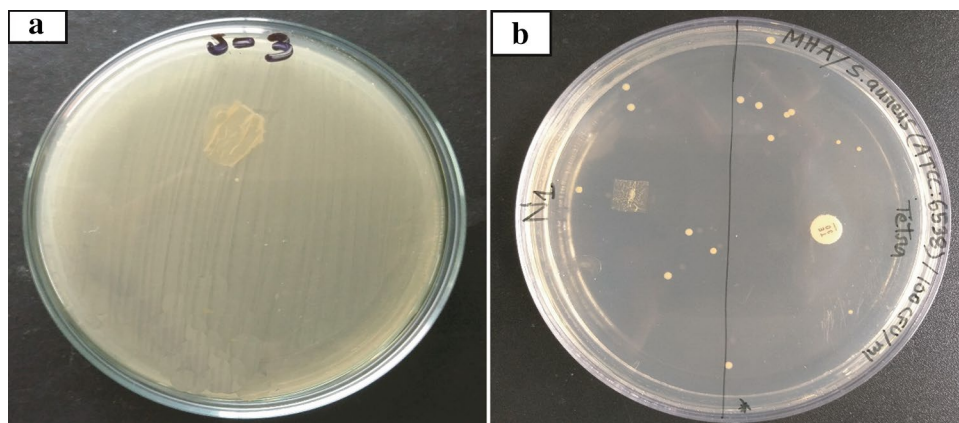

Fig. 5 Observational peaks of neem leaf, N1, N2, N3, N4 and PVA nanomat respectively

insight into the exact mode of action of bioactive compounds of neem extract against Gram-positive bacteria.

FTIR Spectroscopy

Infrared spectroscopy confirmed the presence of PVA polymer and neem constituents in all samples as shown in Fig. 5.

The characteristic peak of neem leaves in FTIR spectra has been identified at a wave number of 2856 cm^{-1} (C–H

stretching) and 1720 cm^{-1} (C=O stretching). Besides, the attributable peaks of PVA polymer have been found at 3433 cm^{-1} (O–H stretching), 2927 cm^{-1} (C–H stretching) and 1095 cm^{-1} (C–O–C stretching). This is in accordance with the signature peaks of PVA and neem as reported in the literature [60, 61]. The presence of free hydroxyl groups and electronegative oxygen in Azadirachtin molecules interact with the hydroxyl group of PVA polymer chains and thus form H-form between them. The probable mode of forming H-bond among these groups has been shown in Fig. 6.

Conclusion

In this research, an optimum processing condition for the fabrication of PVA-neem nanofibrous mats from PVA and neem mixture have been presented. Here, PNNM was developed by electrospinning method with different mixing ratio and then they were characterized. The result of FTIR confirmed the presence of PVA and neem compounds by showing their characteristic peaks. Besides, at optimum conditions fiber was formed having diameter of 173.33 ± 27.95 nm. The PVA-neem nanofibrous mats especially prepared from 80:20 (Neem:PVA) solution ratio exhibited enhanced moisture management and thermal properties. Due to the presence of antibacterial constituents of neem extract, the developed samples showed the formation of inhibition of 20 mm whereas no inhibition zone was formed for PVA nanofiber alone for the same bacteria.

Fig. 6 Proposed mode of H-bond formation between PVA and Azadirachtin
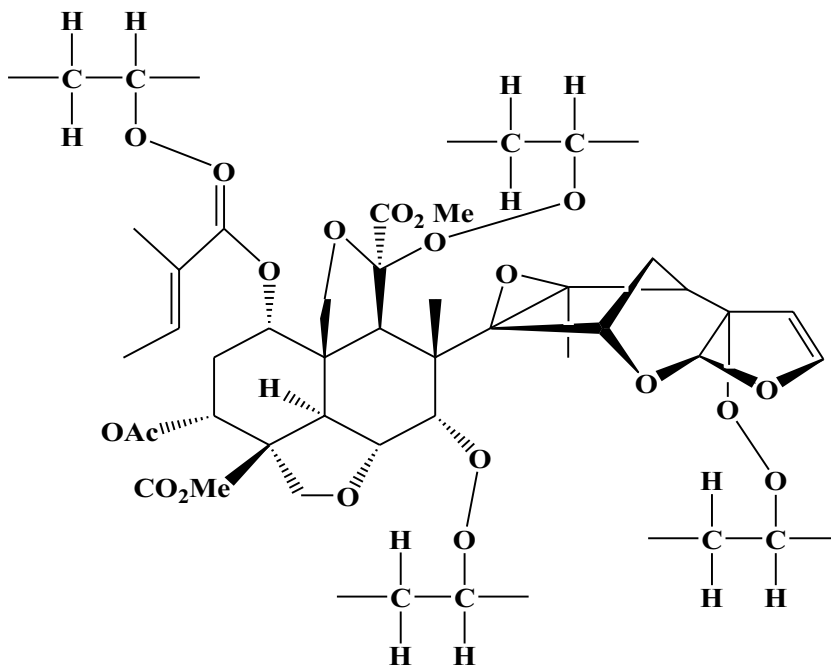
Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author declares that there is no conflict of interest.

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