Controlled release of borneol from nano-fibrous poly(L-lactic acid)/ cellulose acetate butyrate membrane

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Abstract

Borneol, one of the commonly used Chinese medicines, can be used to treat many diseases. The main ingredient of natural borneol is d-borneol extracted from the volatile oil of dipterocarp trees. Numerous studies have proved the effectiveness of borneol. It has been widely used in relieving symptoms of anxiety, fatigue and insomnia; inducing anaesthesia and analgesia to alleviate abdominal pain, wounds and burns; relieving rheumatic pain, hemorrhoids, skin diseases and ulcerations of the mouth, ears, eyes or nose; treating sore throats and skin infections; and is mainly used to treat cardiovascular and cerebrovascular diseases. Although borneol has a significant therapeutic effect, its easy sublimation and low water absorbability make it difficult to control the efficiency of delivery and decrease its function in connecting to various applications in the needs of modern society. Electrospun nanofiber has been commonly used as a delivery vehicle for various medicines for biomedical applications. Poly(L-lactic acid) and cellulose acetate butyrate (CAB) nano-fibrous nonwoven membranes were electrospun and used as drug carriers for borneol. To load borneol into a PLLA/CAB composite membrane, borneol/acetone solution was sprayed on PLLA/CAB fibers. While part of the CAB was dissolved by acetone, borneol was combined with CAB by hydrogen bonds between hydroxyl and carbanyl groups. PLLA still kept a porous morphology of the whole drug-loaded membrane since it does dissolve in acetone. This structure provided a high quality and stable drug delivery system. With adjustable drug release properties, PLLA/CAB nano-fibrous composite nonwoven membranes can be alternative candidates for developing novel external medical textiles.

Keywords

borneol, drug release, electrospinning, poly(L-lactic acid), cellulose acetate butyrate

Borneol, a monoterpenoid alcohol, is the main component derived from *Dryobalanops aromatica* (a species of plant belonging to the teak family). The

main ingredient of natural borneol is d-borneol, which is extracted from the volatile oil of dipterocarp trees. Numerous studies have proved the effectiveness of borneol.[1] It has been widely used in relieving symptoms of anxiety, fatigue and insomnia; inducing anesthesia and analgesia to alleviate abdominal pain, wounds and burns; relieving rheumatic pain, hemorrhoids, skin diseases and ulcerations of the mouth, ears, eyes or nose;, to treat sore throats and skin infections, and is mainly used to treat cardiovascular and cerebrovascular diseases. It can promote drugs' percutaneous absorption, and affects drug pharmacokinetics. Studies also show that borneol can improve the biocompatibility of drugs, improve drug absorption, accelerate the opening of the blood–brain barrier, maintain a steady drug concentration, extend the effect in plasma, and enhance the distribution of drugs in brain tissue. Borneol has a significant therapeutic effect on sciatica and postherpetic neuralgia: both the area of pain and the degree of patients' pain were significantly reduced.[2] However, easy sublimation or evaporation of borneol in the air makes it difficult to control the efficiency of delivery and decreases the function of borneol.[3] Moreover, this inefficient application acquires more powder/unguent than needed, and causes inconvenience for patients when applying the ingredient onto the affected area or controlling the drug dose.

In order to increase the drug efficiency of borneol, more and more attention has been paid to the loading of borneol. A general physical technique for the inclusion of borneol with cyclodextrin or its derivative has been studied to increase the solubility of borneol in water, prevent its evaporation and reduce irritation.[4] In contrast with physical methods, a chemical method via the esterification of borneol was also studied, with small organic molecules and with polymeric materials.[5]

In recent years, electrospinning has been widely used to make ultrafine fibers with small diameters and large surface areas. Electrospun nano-fibrous nonwoven polymers with proteins or other growth factors have been used as a natural extracellular matrix for tissue engineering to promote cell adhesion, migration and proliferation.[6,7] Some drugs were also added into polymer nanofibers for slow-rate controlled drug release and wound dressings.[8]Recently, nanofibers from various synthetic polymers have been electrospun as drug carriers, including poly(L-lactic acid) (PLLA), poly(lactic glycolic acid) (PLGA), cellulose acetate butyrate (CAB),

cellulose acetate, etc. Borneol and polyvinylpyrrolidone (PVP) and shellac nanocomposites were electrospun to enhance drug dissolution rates and improve drug physical stability.[9,10] There are carbanyl groups along the CAB main chain that can bond with borneol to decrease its sublimation. Therefore, in this paper, PLLA/CAB composite nano-fibrous composite membranes were developed as borneol carriers. The drug release process was monitored and discussed. With adjustable drug release properties, PLLA/CAB nano-fibrous composite nonwoven membranes can be alternative candidates for the development of novel external medical textiles (Figure 1).

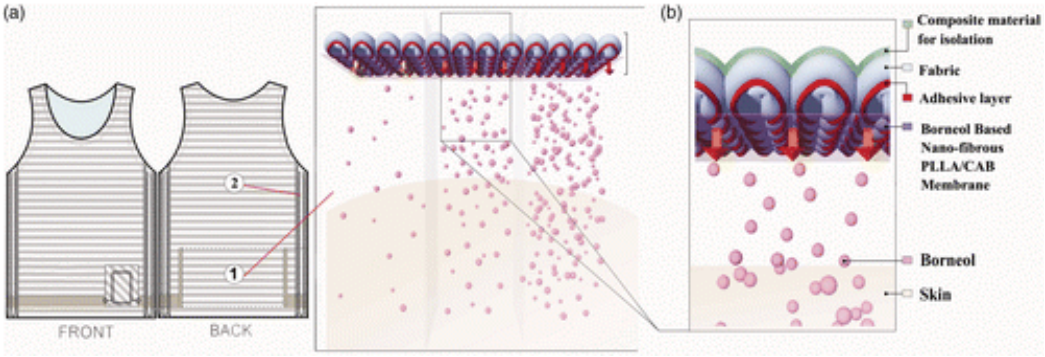

Figure 1. (a) Proposed textile and apparel system for the application of borneol-based nano-fibrous PLLA/CAB membrane. 1 The proposed borneol layer, which is in direct contact with the skin. 2 Two zippers are located on each side of the knitwear so that the knitwear can be tightened or relaxed by either zipping or unzipping. (b) Borneol-based nano-fibrous PLLA/CAB membrane.

Experimental design

Materials

Borneol with purity over 95% was purchased from Anhui, China. PLLA with an inherent viscosity of approximately 7.11 dl/g was purchased from PURAC (The Netherlands). CAB, butyryl content 35–39%, was purchased from Acros Chemical Co. (Pittsburgh, PA).

Cellulose acetate butyrate/borneol composite film

CAB (1.0 g) and 1.0 g borneol were added to 9.0 g acetone. After the CAB and borneol were fully dissolved, the solution was poured onto a glass plate. After the sample was dried, a CAB/borneol solid film was obtained with a thickness of 200 μm.

Electrospinning

- Pure PLLA nanofibers: 1 g PLLA was dissolved by stirring in 100 g chloroform at 50°C. Acetone (10 g) was added to the PLLA solution. The electrospinning solution was loaded into a syringe with a metal capillary connected to an electric power source (12 kV). The syringe's feed rate for the suspension was set to 1.0 ml/hour. The distance between the capillary and the receptor, a grounded aluminum foil, was 15 cm.
- PLLA/borneol composite fiber: borneol was added to a PLLA solution (mass ratio 1:1). Mechanical stirring was applied for 1 h to obtain homogeneous co-dissolved spinning solutions. PLLA/borneol composite nanofibers were then prepared through the electrospinning process as described above with the same parameters as for pure PLLA nanofibers.
- PLLA/CAB composite fibers: CAB was added to a PLLA solution. Three types of spinning solution with various concentrations of CAB (30%, 50% and 70%) were prepared.
- PLLA/CAB/borneol composite: borneol is dissolved in acetone (10% in weight). Borneol/acetone solution was sprayed uniformly onto the PLLA/CAB nano-fibrous membrane. Samples were dried, and kept under seal in cool and dry conditions until further analysis of character. The drug content of each sample was 50% in weight.
- Character: the morphology of the electrospun PLLA/CAB fibrous membranes and borneol-loaded samples were observed using a field emission scanning electron microscope (FESEM, JEOL JSM-6490) at 5.0 kV. Borneol, PLLA, CAB and drug-loaded samples were examined by Fourier transform infrared spectroscopy (FTIR) (Nicolet 5700, Thermo, USA) over the range 500–4000 cm^{-1} with a resolution of 4 cm^{-1}.

Drug release

To determine the effect of CAB, PLLA and PLLA/CAB in controlled release borneol, a comparison study was conducted. Samples containing 25 mg borneol were placed on Petri dishes at 32℃ ± 1℃, similar to skin surface temperature.[11] For each sample, five specimens were weighed every hour.

Results and discussion

Electrospinning poly(L-lactic acid)/borneol

Nano composite fibers have been widely used to control drug release. Generally, the drug was dissolved in the electrospinning solutions with specific polymers as carriers. During the electrospinning process, the polymer and drug mixed in a polymer fiber while the solvents evaporated. In contrast, the electrospun nano-fibrous membrane, with a highly porous structure, exhibits a much greater surface area than the conventional film-casting film. The drug was distributed uniformly along the nano/micro polymer fibers that could allow drug molecules to diffuse out from the matrix much more conveniently[12,13] when these fibrous materials are used as carriers for the delivery of drugs. This strategy is used especially for some drugs that are insoluble in water, such as borneol, 5-Fu and curcumin.[8,9,14,15]

Using the similar electrospinning process and parameters, pure PLLA and PLLA/borneol nano/micro fibers were fabricated (Figure 2). Although borneol did not obviously decrease the spinnability of the PLLA/borneol composite, lots of spindles were found along the PLLA/borneol fibers (Figure 3(c) and (d)). In contrast, the diameter of the pure PLLA fibers had no large change (Figure 3(a) and (b)). Meanwhile, some small holes were observed on the surface of the PLLA/borneol fibers.

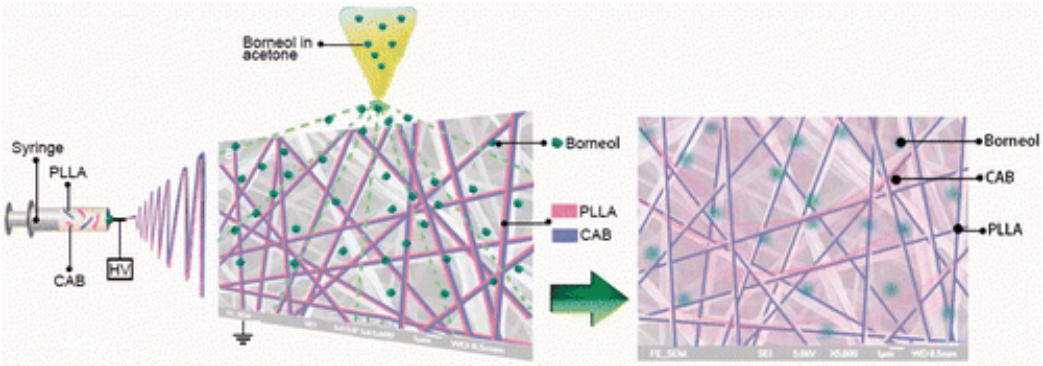

Figure 2. The proposed procedures of the experimental design. After PLLA and CAB were electrospun into a fibrous membrane, borneol/acetone solution was sprayed onto the composite fibers. While CAB was partially dissolved, borneol combined with CAB through hydrogen bonds. Meanwhile, PLLA still supported the porous structure because it does not dissolve in acetone.

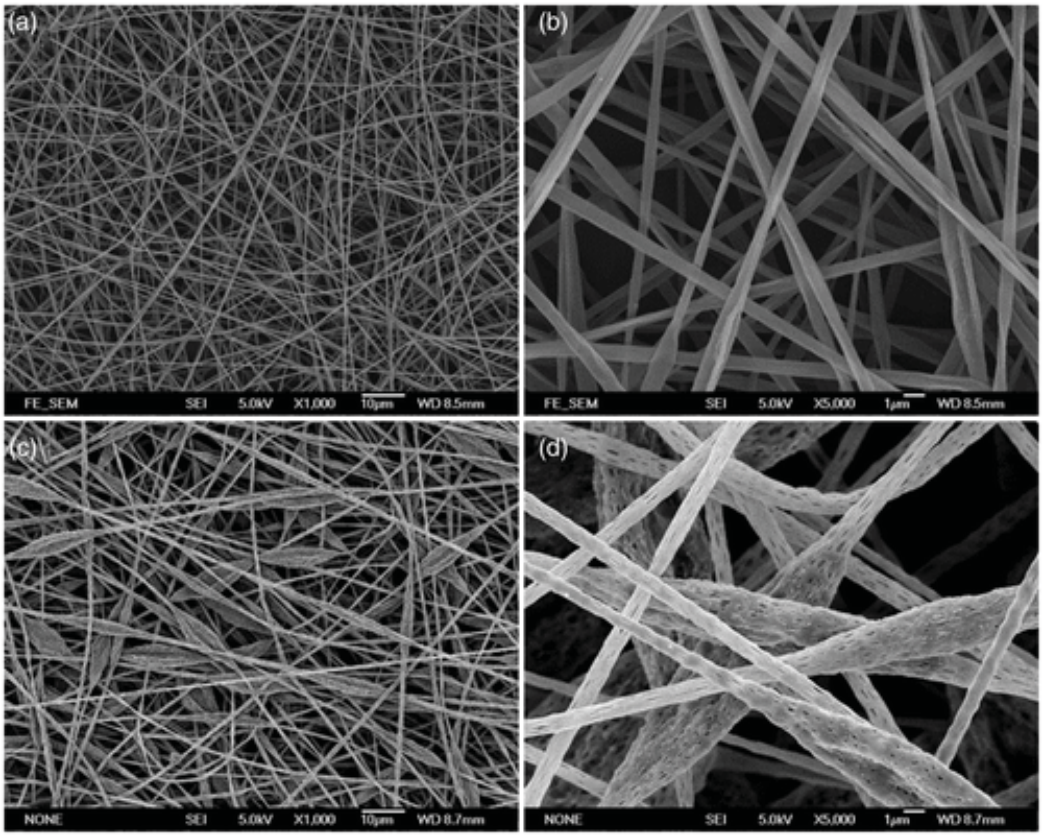

Figure 3. (a, b) SEM of electrospun pure PLLA fibers; (c, d) PLLA/borneol composite fibers.

In order to further confirm the borneol in the composite fibers, the PLLA/borneol fibers were examined by FTIR (Figure 4). The characteristic absorption bonds of camphol (2956 cm^{-1}, 1479 cm^{-1} and 1388 cm^{-1}) are considered as showing that borneol has been detected. However, no characteristic peaks for borneol could be detected after PLLA and borneol were electrospun together. In contrast, borneol could be clearly detected from the PLLA/borneol casting film from the same electrospinning solution. From this, we can conclude that all, or at least most, of the borneol volatilized during the electrospinning process.

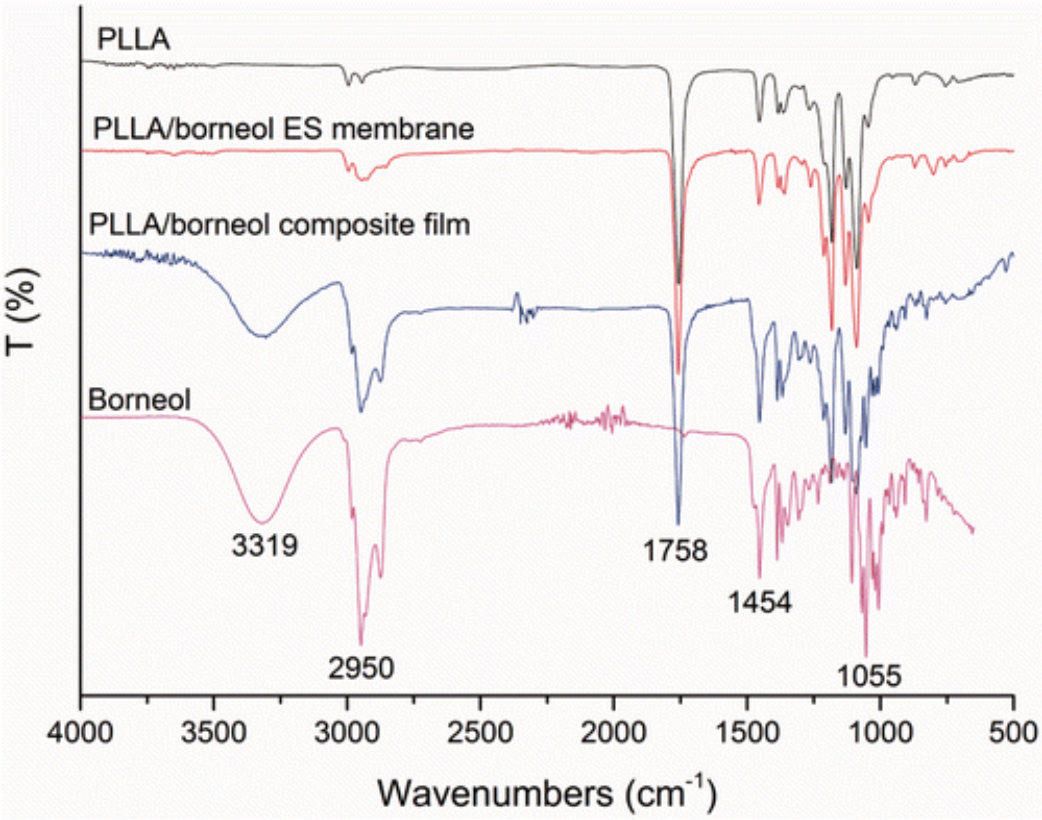

Figure 4. FTIR of pure PLLA, PLLA/borneol electrospun (ES) membrane, PLLA/borneol cast film and borneol.

In the electrospinning process a high voltage is used to create an electrically charged jet of polymer solution from the metal syringe needle. Under a high electric field, the fluid is ejected from the tip of the Taylor cone while a critical value is attained with which the repulsive electrostatic force overcomes the surface tension. The discharged polymer solution jet undergoes an instability and elongation process, which allows the jet to become very long and thin. Meanwhile, before reaching the collecting screen, the solvents of the polymers evaporates, and dry, or at least semi-dry, polymer fibers are left, and are collected as a nonwoven mat.[16] Together with the solvents, borneol also evaporated during the electrospinning process. No borneol could be detected in the final polymer fibers. Since there is no strong interaction between PLLA and borneol, the drug easily escaped from the nonwoven polymer.

Cellulose acetate butyrate/borneol composite

As a family of natural polymeric polysaccharides, cellulose and its derivatives are widely utilized. Hydroxyl groups of cellulose can be modified chemically to form esters or ethers that differ in physicochemical properties, such as in hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate (CA), cellulose acetate butyrate (CAB) and many others. Cellulose esters provide a number of advantages when in membrane form, as some of the membranes can perform controlled-rate drug release.[17] CAB exhibits good solubility in organic solvents, while being hydrophobic.

The compatibility between drugs and carriers is essential for producing high quality and stable drug delivery system. Different components might be combined together because of favorable interactions such as hydrogen bonding, electrostatic interaction and hydrophobic interactions.[18] Each borneol molecule has one hydroxyl group whereas CAB molecules have numerous carbanyl groups. It can be beneficial for the carboxylate oxygen to bond with hydroxyl hydrogen to decrease the runaway of borneol (Figure 5).

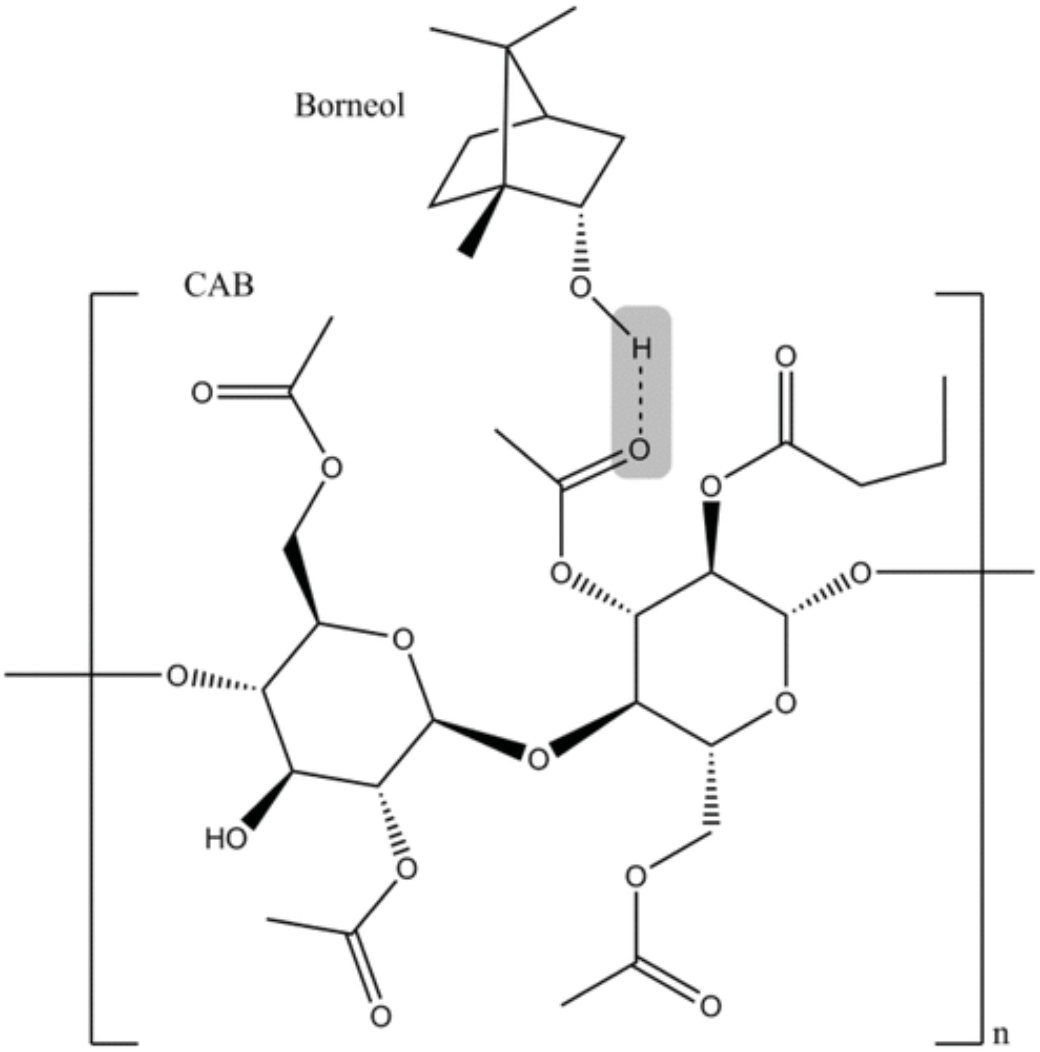

Figure 5. Molecular structure of CAB and borneol and the hydrogen bonding between them.

FTIR spectra of the original CAB membrane indicates a broad hydroxyl peak centering around 3400–3600 cm^{-1}, and a carbonyl peak at 1740 cm^{-1}.[19] Because of its combination with borneol, the maximum absorbance of O–H stretching broadens and shifts to lower wavenumbers from 3100 cm^{-1} to 3700 cm^{-1}, suggesting the formation of the intramolecular hydrogen bond (Figure 6).

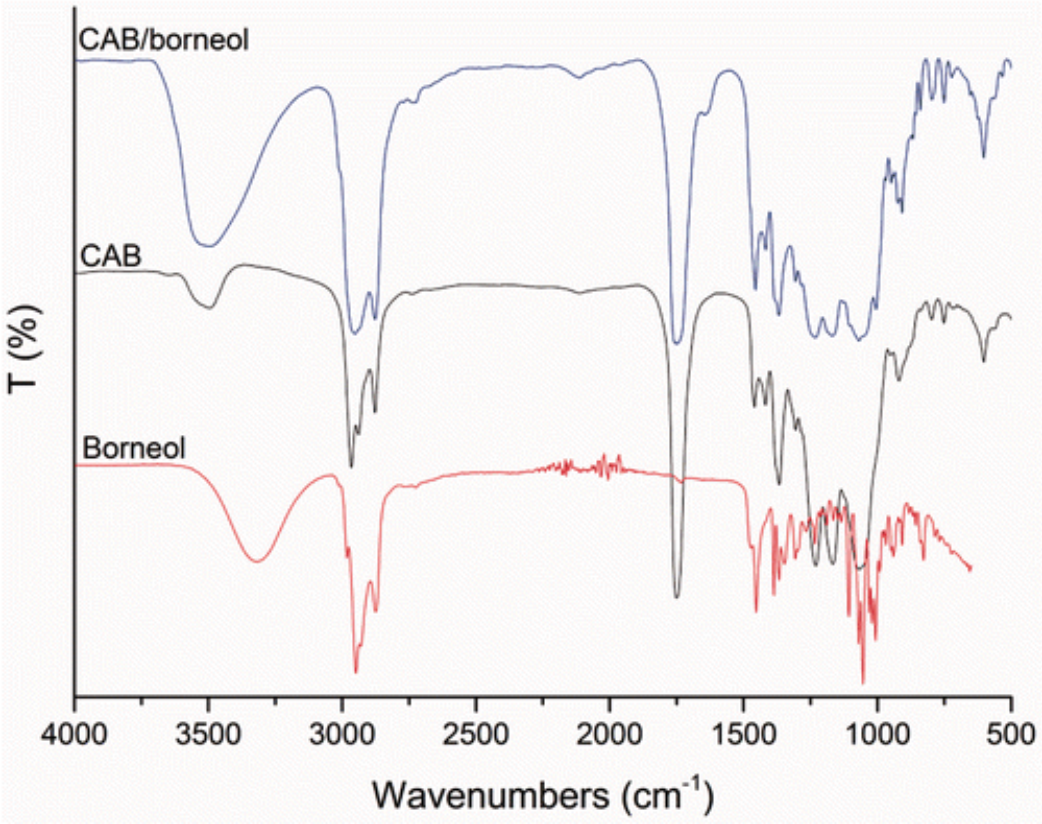

Figure 6. FTIR of borneol, CAB and CAB/borneol composite film.

For a drug delivery system, the membrane characteristics such as morphology, permeability or structure can significantly affect the release of a drug from the film. More importantly, the release speed must match the medication cycle. Either too slow or too fast drug delivery may have negative effects on wound healing. For a CAB/borneol film, the release of borneol from the cast composite film might be too slow. The peak area from 3100 cm^{-1} to 3700 cm^{-1} decreases slightly with time as the borneol is released from the composite film (Figure 7(a)). More than 80% of borneol was left in the film after 8 h (Figure 7(b)). In addition to hydrogen bonds, the solid film also prevented the diffusion of borneol molecules.

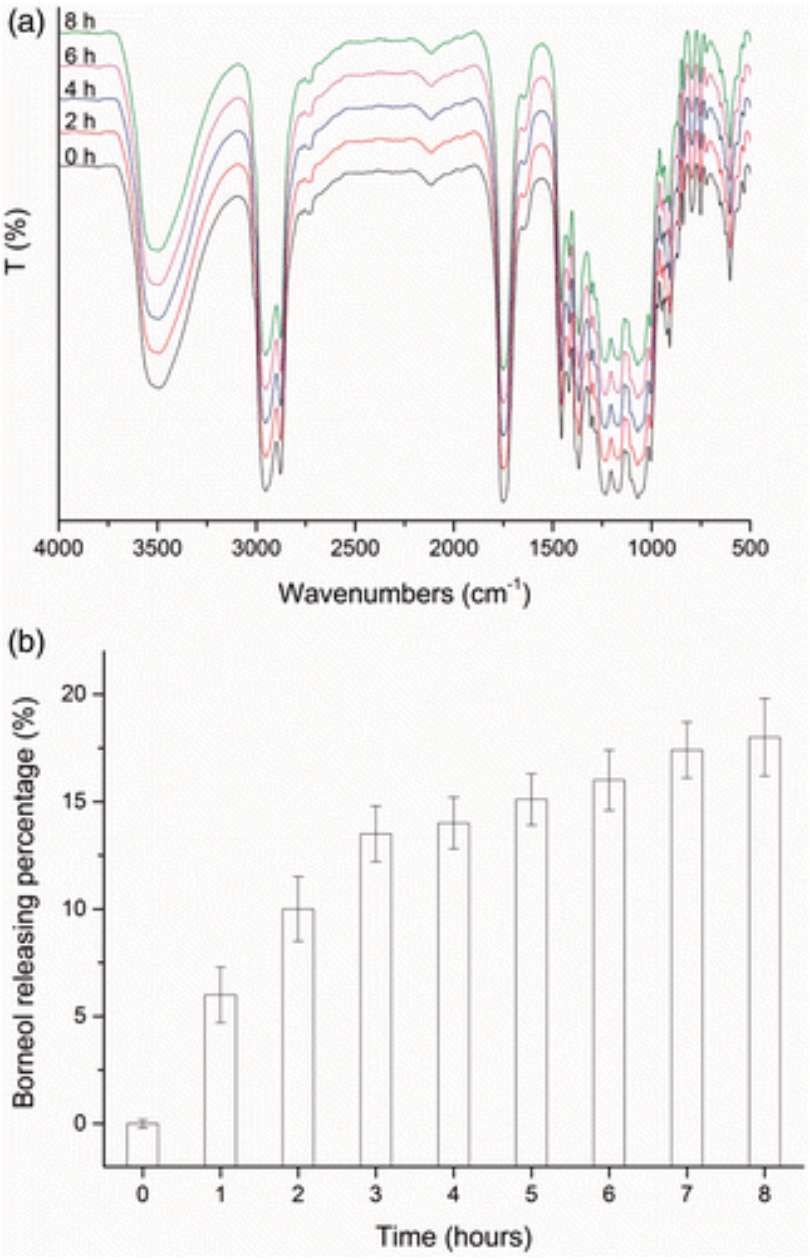

Figure 7. (a) FTIR of CAB/borneol film at different release times; (b) percentage borneol released over time.

Poly(L-lactic acid)/cellulose acetate butyrate nano-fibrous substrate

To tailor the borneol release speed, PLLA/CAB nano-fibrous membranes were carefully designed. First, PLLA/CAB composite fibers with different ratios (0%, 30%, 50% and 70% CAB in weight) were electrospun into nonwoven membranes (Figure 8(a), (c), (e), and (g)). Borneol/acetone solution was then sprayed onto PLLA/CAB

membranes. While borneol solution infiltrated PLLA/CAB fibers, part of the CAB was dissolved by acetone. It formed a thin film among the PLLA fibers and on the surface of the membrane (Figure 8(d), (f), and (h)). Meanwhile, CAB combined with borneol after the acetone evaporated. For a pure PLLA membrane, the fiber shrinked after treatment, while no extra film could be found between PLLA fibers since it does not dissolve in acetone. For PLLA/CAB composite membranes, PLLA helped to keep the porous structure that is beneficial for the diffusion of borneol.

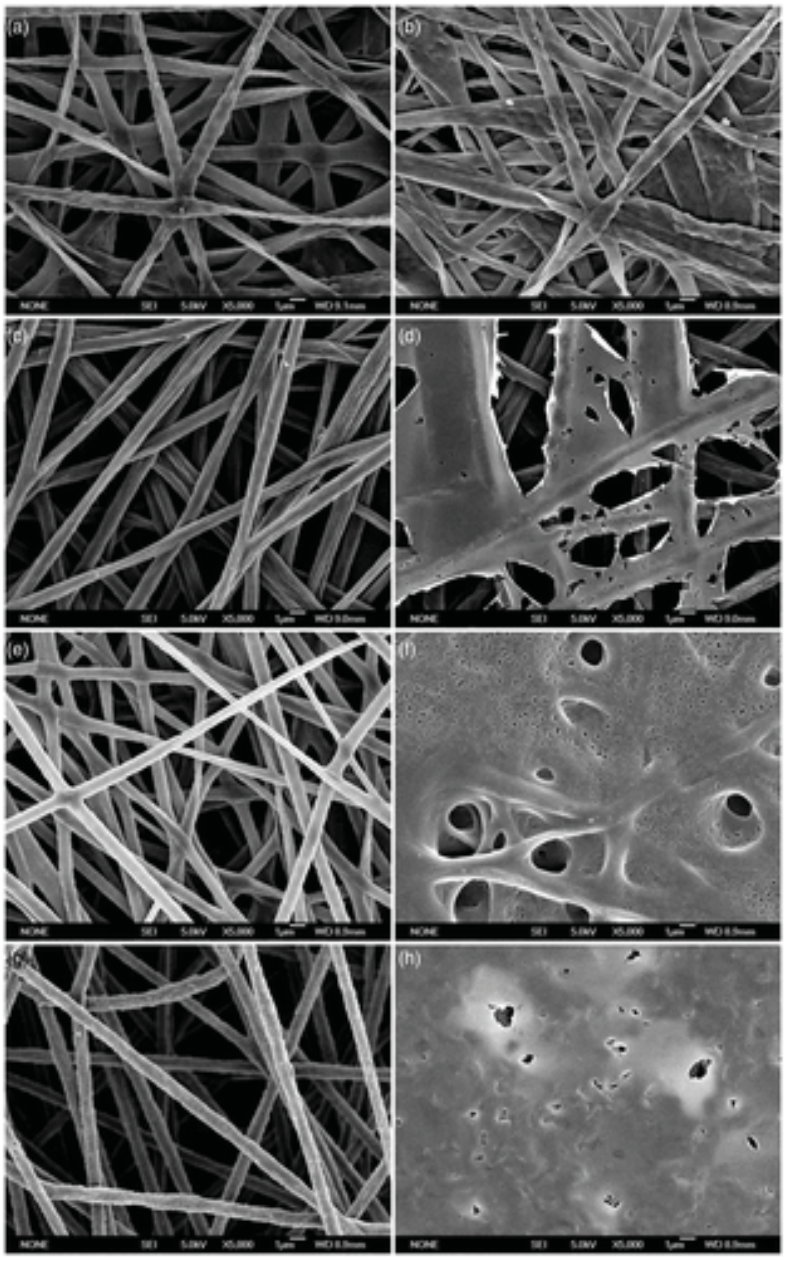

Figure 8. SEM of (a), (b) pure PLLA; (c), (d) PLLA/CAB (30% CAB in weight); (e), (f) PLLA/CAB (50% CAB in weight); (g), (h) PLLA/CAB (70% CAB in weight) nanofibers before and after acetone treatment, respectively.

Shown in Figure 9 is the drug release of borneol from pure PLLA and PLLA/CAB with different ratios. For pure PLLA, more than 70% of the borneol was lost in the first hour because there was no interaction between PLLA and borneol. Moreover, the borneol molecules were dispersed uniformly on the surface of PLLA fibers, which accelerated its emission. The emission was even faster than for pure borneol particles on a Petri dish.[9] For PLLA/CAB composite fibrous membranes, more and thicker CAB films were formed between PLLA fibers and on the surface of the membranes, as hydrogen bonding between CAB and borneol effectively decreased drug sublimation from the composite membranes. The adjustable porous structure of PLLA/CAB also played an assistant role controlling the drug release speed. For PLLA/CAB (30%) membrane, the releasing of borneol decreased dramatically compared to pure PLLA. But for PLLA/CAB (70%), more than half of the borneol was still left in the membrane due to the low porosity.

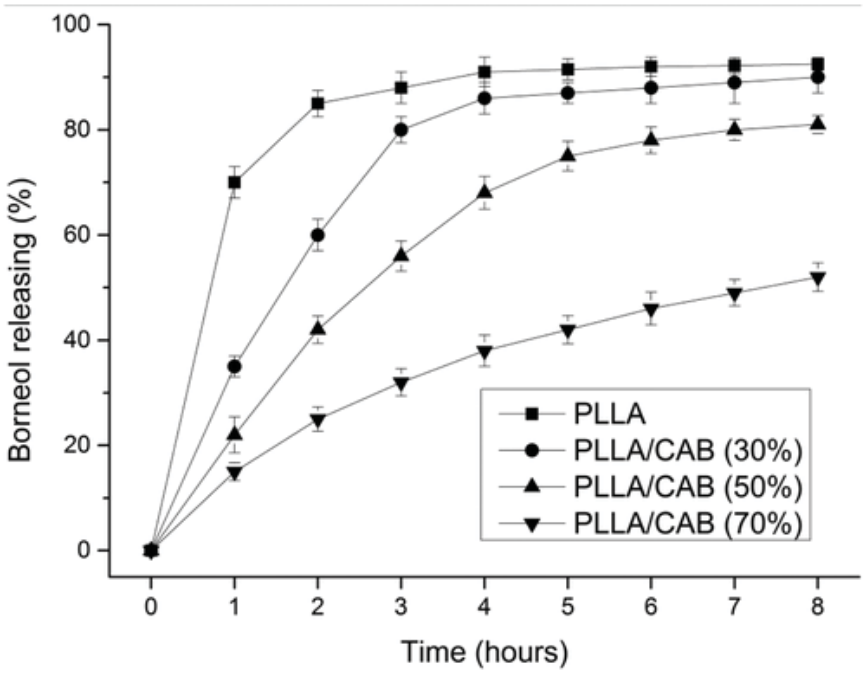

Figure 9. Drug release of borneol for pure PLLA and PLLA/CAB composite membranes (30%, 50% and 70% CAB in weight).

Conclusions

Due to the fast sublimation of borneol, simple electrospinning was not a practical method to load polymer nanofibers with the drug. Therefore, PLLA/CAB nano-fibrous nonwoven membranes were electrospun as borneol carriers. When borneol/acetone solution was added to the PLLA/CAB composite fibers, part of the CAB was dissolved and combined with borneol through hydrogen bonds that effectively enhanced borneol's physical stability against sublimation. In contrast, PLLA still kept the porous morphology of the whole drug-loaded membrane since it does dissolve in acetone. This structure provided a high quality and stable drug delivery system. With adjustable drug release properties, PLLA/CAB nano-fibrous composite nonwoven membranes can be alternative candidates for developing novel external medical textiles.

Declaration of Conflicting Interests

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