Cellulose Nanocrystals for Skin Barrier Protection by Preparing a Versatile Foundation Liquid

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ABSTRACT: Most of the foundation liquids in the market need makeup removers for cleaning, while the excessive use of makeup removers might lead to skin barrier damage, which would further lead to many kinds of dermatosis, such as skin sensitivity, facial telangiectasia, rosacea, acne, as well as various cosmetic contact dermatitis. Inspired by the protective effect of fiber-rich diet on the intestinal mucosal mechanical barrier, a novel hemp/cellulose nanocrystals (CNCs)-based foundation liquid featuring easy-wiping property has been constructed, which will effectively solve the post-makeup skin cleaning problems. In this experiment, the formula of the foundation liquid can be obtained through hemp/CNCs instead of mineral oil and titanium oxide, which are considered to have undesirable local tolerance, sensitizing potential, and are environmental pollutants, to create a moisture barrier. Industrial hemp is a hot issue in cosmetic research, and a great quantity of discarded industrial hemp stalk is available to be used to produce hemp/CNCs through grinding and cellulose on whey protein isolation, digestion of starch and cellulose can protect intestinal mucosa through the removal of excessive fat, protein, and sugar in the intestinal tract, as shown in Scheme 1. Inspired by this phenomenon, can we find new strategies taking advantage of the "removal" feature of cellulose to design a foundation liquid? Cellulose can be derived from a variety of sources, such as wood (hardwood and softwood), seed fibers (cotton, coir, etc.), bast fibers (flax, hemp, jute, ramie, etc.), grasses (bagasse, bamboo, etc.), marine animals (tunicate), algae, fungi, invertebrates, and bacteria. As one of the earliest fibers used by human beings, the waste hemp stalks can be reused, which in the meantime can conserve resources and protect environment. With the natural emulsifying and stabilizing characteristics, hemp cellulose is

INTRODUCTION

Foundation liquid, used as a makeup base of cosmetics, can let the cosmetic materials firmly adhere to the skin and, at the same time, beautify the facial skin color and defects, improving the look of the skin texture. However, after using the commercial foundation liquid (CFL), it is necessary to use makeup remover oil or other cleaning products which could damage the skin barrier, which might lead to many kinds of dermatosis such as skin sensitivity, facial telangiectasia, rosacea, acne, and various cosmetic contact dermatitis. Therefore, it is imperative to find a new alternative material that avoids the skin barrier damage caused by excessive cleaning.

Recently, with the legalization of industrial hemp around the world, more researchers have focused their attention on this material. According to the reports, hemp has been discovered for cleaning, while the excessive use of makeup removers might lead to skin barrier damage, which would further lead to many kinds of dermatosis, such as skin sensitivity, facial telangiectasia, rosacea, acne, as well as various cosmetic contact dermatitis.
Scheme 1. Schematic Illustration of Protective Effect of Cellulose on the Intestinal Barrier through Removal of Fat and Bile Salts in Intestine Digestion and How It Inspired the Development of a Foundation Liquid that Protects the Skin Barrier with Similar Cellulose

Figure 1. (A) Schematic illustration of preparing hemp/CNCs-g-PLA; (B) FTIR spectra of the commercial cellulose, hemp/CNCs, and hemp/CNCs-g-PLA; (C) AFM morphological images (2 μm × 2 μm) of hemp/CNCs and hemp/CNCs-g-PLA as well as their respective particle size (length and width) distribution.
intermolecular hydrogen bonds that naturally exist within, which profoundly limits the application of CNCs. Thus, many investigators are trying to learn more about the properties of natural and modified CNCs.

Polylactic acid (PLA) is considered the pioneer of biodegradable polymers, which can be hydrolyzed in the human body by acids or enzymes to produce lactic acid. Lactic acid, a cell metabolite, can be further metabolized by enzymes in the body, producing CO₂ and H₂O as the reaction result. Therefore, PLA is non-toxic and harmless to the human body with good biocompatibility and bio-absorbability. It has also been approved by the FDA of the United States to be used as a biological material for implantation in humans. Because of its excellent biocompatibility, biodegradability, renewability, good mechanical strength, and facile production method, the PLA was grafted with the hemp/CNCs to produce hemp/CNCs-PLA.
PLA that enjoyed a better dispersion in both aqueous and oil solutions. The foundation liquid based on the hemp/CNCs-g-PLA that was impermeable and easily wiped was prepared, providing an alternative cosmetic product to avoid skin damage caused by excessive cleaning.

RESULTS AND DISCUSSION

Characterization. Fourier Transform Infrared Spectra of Hemp/CNCs, Hemp/CNCs-g-PLA, and Commercial Cellulose. Confirmed by the Fourier transform infrared (FTIR) spectrum, the grafting modification of the hemp/CNCs with PLA was successful. Figure 1B shows the FTIR spectra of hemp/CNCs-g-PLA, hemp/CNCs, and commercial cellulose. The FTIR spectrum of hemp/CNCs revealed characteristic functional groups, a specific absorbency of O–H stretching around 3400 cm$^{-1}$ (3200–3600 cm$^{-1}$), weak C–H stretching around 2930 cm$^{-1}$, C–H bending around 1420 cm$^{-1}$, and C–O–C bending at 1020 cm$^{-1}$. A stretching of C–O–C and C–O at 1000–1200 cm$^{-1}$ corresponded to the presence of carbohydrates. At the same time, there was no peak near the 1700 cm$^{-1}$, which represented the C=O stretching, indicating that the extracted hemp/CNCs did not contain pectin. The C=C symmetric telescopic vibration absorption peak in the lignin aryl group was also not found near the 1508 cm$^{-1}$. Therefore, the disappearance of these two wave numbers indicates that pectin, lignin, and other impurities were removed during the preparation of hemp/CNCs. 22 However, hemp/CNCs-g-PLA showed a strong absorption peak near 1700 cm$^{-1}$, which represented C=O stretching of the ester bond created after grafting PLA on hydroxyl groups of hemp/CNCs, indicating that the PLA had been attached to the hemp/CNCs. Besides, near 1400 cm$^{-1}$, the absorbency of hemp/CNCs-g-PLA was lower than those of hemp/CNCs and commercial cellulose, which indicated that some hydroxyls of C6 was oxidized during the modification of hemp/CNCs. The oxidation of hydroxyls of C6 would help to improve the dispersion of hemp/CNCs-g-PLA.

Atomic Force Microscopy Images of Hemp/CNCs and Hemp/CNCs-g-PLA. The morphology was analyzed by atomic force microscopy (AFM), which can provide 3-D information (X, Y, and Z) of the test samples. Figure 1C shows AFM images of both hemp/CNCs and hemp/CNCs-g-PLA. In general, the overall morphology of hemp/CNCs was retained throughout the multi-step procedure. The particles had average dimensions of 300 nm × 50 nm × 6 nm, as revealed by statistical measurements based on AFM images. In vivo studies have discovered that CNCs with length from 5 to 70 nm and width from 150 to 2100 nm are harmless to the human body. 23 Besides, it is also shown that CNCs are nontoxic to endothelial cells of human brains and hardly exhibit any nonspecific cellular uptake. 24 The morphology of CNC rods was found to be similar to what has been previously described. 25 The mean dimensions (section of 5–6 nm, length (X) of 300 nm ± 80 nm, and width (Y) of 60 ± 20 nm) were estimated based on the AFM images by statistical analysis of the cross-section profiles of each rod of dilute nanocrystal suspensions deposited on a silicon wafer. Molecular structure of CNCs contains hydroxyl groups that could easily form intermolecular hydrogen bonds, 10,26 which would result in agglomeration and larger particle size of CNCs. The hemp/CNCs-g-PLA was obtained by grafting, which reduced the quantity of hydroxyl groups, weakened the intermolecular force, and improved the dispersion, so that the dispersion of the foundation liquid became better. As shown in Figure 1C, in hemp/CNCs-g-PLA, the percentage of particles with length smaller than 300 nm and width shorter than 75 nm is higher than that of hemp/CNCs.

In summary, as per the results of characterization, the method of graft copolymerization adopted to obtain the hemp/CNCs-g-PLA with improved dispersion was successful.

Cell Toxicity. Safety verification comes before the test of efficacy. The toxicity of hemp/CNCs and hemp/CNCs-PLA on normal HaCaT cell was evaluated in accordance with the CCK-8 assay. As shown in Figure 2B, there was no significant inhibition even at doses of 10 mg/mL. At the same time, the morphological images also showed that the two materials had good biocompatibility with cells, did not change the morphology of cells and had no obvious cytotoxicity, as represented in Figure 2A. With the results of the cytotoxicology, the concentration of hemp/CNCs-g-PLA could reach 10 mg/mL in the following experiment. In addition, the results also showed that the hemp/CNCs-g-PLA was more likely to adhere to cells than hemp/CNCs after being washed with phosphate-buffered saline (PBS) twice, suggesting that it may have better ability of adhesion, as seen in Figure S1.

Stability of Formulations. Both foundation liquid 1 (FL1) and foundation liquid 2 (FL2) were light yellow in color. The pH of FL1 ranged from 5.5 to 6 and that of FL2 ranged from 5 to 5.5 which were suitable for topical application. The stability study showed that FL1 and FL2 were stable during 3 months. The layering phenomenon was not seen in FL1 and FL2 after returning to room temperature.

Penetration of Hemp/CNCs-g-PLA Skin In Vitro. There are still some concerns about the safety of nanoscale materials and uncertainties about their effects once they enter human systems. It is, therefore, necessary to demonstrate the skin serving as a barrier to hemp/CNCs-g-PLA uptake, and hence, the ability of the samples to remain on the stratum corneum were tested. As a type of fluorescent dye, the fluorescein isothiocyanate isomer (FITC) has been used as a probing compound in previous skin penetration studies. 27,28 The effect of skin penetration of the hemp/CNCs-g-PLA labeled by FITC was investigated through a pig skin model, which has been used in a variety of topical applications, including penetration studies for chemicals and nanoparticles. The skins treated with agents (FL1, FL2, and liquid mixed with free FITC) were examined under a fluorescent microscope for FITC skin penetration profiles at different depths. Representative fluorescent microscopic images of skin samples treated with the above three agents are shown in Figure 2D and the data of corresponding depths appear in Figure 2C. The data in Figure 2C indicated that the FL2 mainly remained on the surface of stratum corneum after topical application, without penetration into the cellular epidermis or dermis. Three hours after application, most of the FL2 still stayed on the surface of stratum corneum, while the FL1 demonstrated deeper penetration into the dermis. Based on the above findings, it is speculated that the foundation liquid based on hemp/CNCs-g-PLA would not penetrate into the epidermis and might have protective effects by preventing harmful substances from entering the skin.

Safety of Hemp/CNCs-g-PLA In Vivo. Easy Wiping Properties and Permeability of Hemp/CNCs-g-PLA on Animals. The FL1, FL2, and a gel mixed with free FITC were applied to the dorsal skin of mice and in vivo imaging was performed. The results are shown in Figure 2E,F; the IVIS
images clearly demonstrated that the fluorescent signals of the FITC on gel and FL1 were still well maintained on the dorsal skin after wiping. Consistently, the total removal rate of both FL1 and gel mixed with free FITC is low (Figure 2E), while FL2 showed a remarkable fluorescence removal rate, which suggested that the foundation liquid based on hemp/CNCs-g-PLA had the characteristic of easy wiping.

**Easy Wiping Properties of Hemp/CNCs-g-PLA on Humans.** Dermoscopy was employed to visualize the surface features of original and different states of skin on hand dorsa in order to better understand the easy wiping ability of the foundation liquid based on hemp/CNCs-g-PLA. As presented in Figure 3A, the photographs indicated that skin discoloration and age spots were reduced after using CFL and foundation liquid based on hemp/CNCs-g-PLA while skin roughness was also alleviated. After being wiped with a makeup cotton, the CFL residue in the skin texture could still be seen clearly, while there was little residue in the skin texture after the foundation liquid with hemp/CNCs-g-PLA was wiped. Subsequently, clean water and makeup oil, in such order, were applied for deep cleaning of the skin. The results showed that the skin texture became unclear and some red spots appeared, suggesting that the skin barrier might have been damaged. This further illustrates the importance of easy wiping ability of the foundation liquid for protecting the skin barrier.

**Figure 3.** (A) Surface features of original and different skin states on the dorsum of human hands; (B) schematic diagram of the $L^*b^*$ plane and its corresponding color classification; (C) $L^*$ and $b^*$ values of (I) foundation liquid based on hemp/CNCs-g-PLA and (II) CFL from 1 to 9 h.

**Figure 4.** (A) Retention rates at 1 and 6 h are quantified. Data are presented as the mean with standard deviation ($n = 3$, *p* < 0.05, **p** < 0.01); (B) Foundation liquid mixed with hemp/CNCs-g-PLA-labeled FITC was applied to the dorsal skin of mice, and the skin retention was captured with IVIS at 0, 1, and 6 h.
Efficacy of Hemp/CNCs-g-PLA In Vivo. Adhesion Property of Hemp/CNCs-g-PLA on Animals. The adhesion property of the FL2 to the skin was tested. As shown in Figure 4, the fluorescence stayed on the dorsal skin surface from 1 to 6 h, and the retention rate could be kept above 90%, indicating that the foundation liquid based on hemp/CNCs-g-PLA could provide satisfactory adhesion ability.

Adhesion and Concealer Properties of Hemp/CNCs-g-PLA on Humans. The results of VISIA are seen in Figure 5. The images showed significant improvement in facial acne and apparent pigmentation with foundation liquid based on hemp/CNCs-g-PLA, similar to the cosmetic properties of CFL. The number of pores on both sides of the nose was counted, and the dispersion of the gray value before and after applying the foundation liquid was also measured. The result illustrated that both the number of pores and the dispersion of the gray value decreased after using the foundation liquid based on hemp/CNCs-g-PLA, indicating that the skin color has been visually improved. In addition, the results of the skin individual typology angle (ITA°) showed that the ITA° of the skin was improved from the previous 67° to about 70° after the use of the foundation liquid based on hemp/CNCs-g-PLA. ITA°, a parameter used for skin color typing, represents the overall change in hue. The higher ITA° is, the lighter, whiter, and less...
yellowish the skin color is. The results and data of VISIA images showed that the foundation liquid based on hemp/CNCs-g-PLA was effective in concealing skin defects and unifying skin color, which meets the basic requirements of a foundation solution.

Meanwhile, the adhesion property of the foundation liquid based on hemp/CNCs-g-PLA was assessed through changes in $L^*$ and $b^*$ values every hour in the 9 h after application. As shown in Figure 3C, without noticing significant changes in $L^*$ and $b^*$ values of the new foundation liquid during this period, the lightness and skin color basically remained on the same plane. The results showed that the new foundation liquid adhered well to the skin surface within 9 h, during which time the skin surface was maintained with stable gloss and uniform colors. At the same time, the CFL represented similar results as a reference as shown in Figure 3C (II), indicating that the foundation liquid based on hemp/CNCs-g-PLA had a similar adhesion property to that of CFL.

## CONCLUSIONS

This study provides a new green alternative material for the current cosmetic industry as well as an innovative way to reuse waste hemp stalks through a simple maneuverable producing process. On the premise that safety is guaranteed, the foundation liquid prepared with hemp/CNCs-g-PLA meets the adhesion requirements (good makeup durability) of foundation liquid, with additional features such as good concealing feature, improved dispersion, non-penetration into skin, and easy wiping. The easy-wiping property can avoid secondary damage to the skin caused by cleansing products such as makeup remover. In addition, because of the adsorption effect of cellulose, wiping the foundation liquid prepared by hemp/CNCs-g-PLA will not damage the skin barrier, which would also take away the excessive oil and air pollutants on the skin surface, just like how cellulose does during the digestion and metabolism in the intestine. The foundation liquid based on hemp/CNCs-g-PLA will undoubtedly bring new development and alternative products to the field of dermatology and cosmetics. It does not only meet the needs of healthy skin for a continuous and healthy use but also brings new benefits to the users whose skin barrier is damaged. They also pose many promising features including superior concealing properties, outstanding flaw-covering function, bedecking pores, long covering efficiencies, and nonirritating nature.

## EXPERIMENTAL SECTION

### Preparation of Hemp/CNCs

The method of hemp/CNCs preparation takes reference to many existing researches. As shown in Figure 1A, hemp stalks and leaves were cut into squares of approximately 1 cm × 1 cm size, before being grinded to pass a 40-mesh screen. The milled powder (50 g) was added into 500 mL of sulfuric acid (60%, w/v) with gentle stirring, and the obtained mixture was heated in a water bath to 45 °C. After 1 h of vigorous stirring at 45 °C with a mechanical stirrer, the reaction was quenched by 10-fold dilution with cold (around 4 °C) deionized water. The suspension was centrifuged at 5000 rpm for 15 min, and the supernatant substances were discarded. The sediment was dissolved again with deionized water. The centrifugation and dissolution process were repeated for 3–5 times. Next, the deposit was transferred to a dialysis tube to dialyze against deionized water until the pH was nearly 7.0. Finally, the sample was heated to 80–100 °C until the weight remained constant, and the remaining powder was the hemp/CNCs.

### Preparation of Hemp/CNCs-g-PLA

As shown in Figure 1A, hemp/CNCs powder (1 g) was slowly added to 50 g NaOH solution (15%, w/v) and stirred for 3 h and l-lactic acid (about 12 mL) was added to adjust the pH value of the solution to about 7. To obtain the powder, the solution was vigorously stirred for another 3 h before being rinsed with deionized water and filtered. The powder was dried in a vacuum oven at 80 °C for 8 h and marked as pre-hemp/CNCs. Then, the pre-hemp/CNCs, 30 mL dimethyl sulfoxide, and 1 g l-lactide were taken in a 100 mL Shrek reaction bottle and the mixture was heated to 110 °C in an oil bath. After thorough dehydration with a vacuum pump, a small amount of Sn (Oct)2 was added followed by stirring for another 6 h of continued reaction. About 10 drops of HCl was added to stop the reaction when the time was up. After a short cooling-down of the solution, 20 mL dichloromethane and 40 mL absolute ethanol were added to the solution, which was then left still overnight and filtered the next day. The above operation was repeated for 3–5 times until no precipitation was observed when absolute ethanol was added to the filtrate. When the solution was dried in a vacuum oven at 80 °C for 24 h to obtain the hemp/CNCs-g-PLA. The process diagram is shown in Figure 1A.

### Hemp/CNCs-g-PLA Labeled by FITC

FITC was used to label hemp/CNCs-g-PLA according to a reported method. Briefly, FITC (10 g, dissolved in ethanol) and hemp/CNCs-g-PLA (500 g, 4 wt %, ethanol as solvent) were mixed under stirring at 50–60 °C for 36 h and the flask was covered with aluminum foil to avoid light. Then, the mixture was transferred to a dialysis tube and dialyzed against deionized water. When diffusion of excessive FITC from the reaction mixture ceased through visual inspection of the dialysis water, the suspension was sonicated under ice-bath for 10 min at 40% output and centrifuged for 12 min at 4550 rpm to remove agglomeration. The supernatant was again dialyzed against deionized water until the dialysis water no longer showed FITC UV-vis absorption peaks.

### Characterization

**FTIR Spectroscopy.** FTIR spectra were recorded with a Shimadzu UV3600 FTIR spectrometer from KBr pellets with a resolution of 0.1 nm and 64 scans per sample. For KBr pellet preparation, the sample was mixed with KBr in a ratio of 1:49, and the final weight was ensured to be approximately 100–120 mg. The obtained powder was pressed by the powder pressing machine (YP-15) to form pellets, which was dried in an infrared lamp at 45–60 °C for several hours until there was no free moisture. Finally, the dried pellets were examined by FTIR.

**Atomic Force Microscopy.** AFM (Bruker dimension icon, Bruker, Germany) analysis was performed to better observe the morphological features of commercial cellulose, hemp/CNCs, and hemp/CNCs-g-PLA. The investigations were performed in peak-force intelligent scanning mode, at room temperature, with a scan rate of 1.0 Hz and a scan angle of 0°. A silicon tip (Scanasyt-air model, elasticity coefficient is 0.4 N/m) on a nitride lever with a cantilever length of 115 μm and a resonance frequency of about 70 kHz was used for the measurements. The image processing and the data analysis were conducted with NanoScope Analysis 1.9.

### Cell Toxicity

Cell proliferation activity induced by hemp/CNCs and hemp/CNCs-g-PLA was examined with the CCK-8 method. The cell proliferation activity was measured using a colorimetric assay with CCK-8 reagents. The samples were incubated for 24 h at 37 °C, and then cell proliferation activity was determined by measuring absorbance at 450 nm using a microplate reader.
Each BALB/C nude mouse was cleaned with alcohol pads and then with free FITC were prepared. Animals were kept in the animal center and given free access to food and water over the duration of the study. For the live imaging, the dorsal skin of each BALB/C nude mouse was cleaned with alcohol pads and subsequently with PBS solutions. Later, FL1, FL2, and 0.1 mm thick gel mixed with free FITC were, respectively, applied on the dorsal skin of mice. The mice were later imaged and quantified by an IVIS (PerkinElmer, Massachusetts, USA). For evaluation of the adhesion property of the foundation liquid based on hemp/CNCs-PLA, the mice were housed individually and imaged at 1, 3, and 6 h after application of the tested materials. For evaluation of mechanical removal of the foundation liquid based on hemp/CNCs-g-PLA, all the tested skins were wiped with a wet towel once. Those mice were subsequently dried and sent for IVIS imaging.

In Vivo Experiments on Humans. The experiments were approved by the institutional ethical committee and performed in compliance with the institutional guidelines at School of Clinical, West China Hospital of Sichuan University. The easy wiping property of the foundation liquid based on hemp/CNCs-PLA was measured by dermoscopic images with a CBS-606 portable dermatoscope (Xiangmei technology, Taiwan, China). Meanwhile, a CFL was chosen as a reference. The experiment involved 20 women volunteers from Chengdu, aged between 22 and 45 with a median age of 25. The foundation liquid based on hemp/CNCs-g-PLA was applied on the back of their hands and dermoscopic images were captured to observe the changes of the skin texture. The dermoscopic images were taken at the following moments: before any procedure (original skin), after using the foundation liquid (skin with the foundation liquid), after wiping with wet towels (scoured skin), after washing with clean water (washed skin), and after washing with cleaning oil (oil washed skin). All images have the same fixed values of aperture, ISO, focus distance, and focal length.

The adhesion of the foundation liquid based on hemp/CNCs-g-PLA was also characterized with the CIE 3D space system of the Minolta spectrophotometer CM-2600d (Minolta Co. Ltd. Osaka, Japan). In this system, any skin color can be represented by three variables that represent skin pigmentation, namely, L* being the lightness axis, a* being the red-green axis, and b* being the yellow-blue axis. The L*, a*, and b* will not change significantly over time and vice versa. Twenty volunteers were involved in the test and had signed the informed consent prior to the test. The front of their faces was photographed with the VISIA-CR (Canfield Scientific, New Jersey, USA) imaging station in UV mode. Foundation liquid based on hemp/CNCs-g-PLA (0.2 mg) and CFL was applied to the entire face before the photographs were captured by a commercial clinical imaging device VISIA-CR camera booth in three modes, which is regarded as the industry standard for repeatable clinical high-resolution imaging.

Statistical Analysis. All experiments were repeated three times (n = 3). Data are presented with means ± standard deviation (mean ± SD) and analyzed by Student’s t-test. p < 0.05 was considered to be significant, and p < 0.01 was considered to be highly significant.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c05257. Adhesion ability of hemp/CNCs and hemp/CNCs-PLA on HaCaT viability (PDF)
Signatures of Contact Dermatitis and Implications for Treatment.

Sichuan University.

1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University.

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