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Enantioselective membranes prepared by electrospinning of cellulose tris-(3,5-dimethylphenylcarbamate) synthesized from hardwood cellulose fibers

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14 Abstract: Cellulose phenyl carbamates such as cellulose tris-(3,5-dimethyl phenyl carbamate) 15 (CDMPC) are known to act as chiral selectors when they are immobilized on silica gels that are 16 packed in the columns for high-performance liquid chromatography (HPLC). Previously, we 17 reported a proof of concept of enantioselective membrane filtration using a nonwoven membrane 18 prepared by electrospinning of the CDMPC synthesized from microcrystalline cellulose Avicel®. In the present work, TECHNOCEL® cellulose fiber samples derived from hardwood are 19 20 functionalized to synthesize CDMPCs having higher and different degrees of polymerizations. The 21 length and width of the cellulose fiber samples are characterized using a MorFi image analyzer. 22 The obtained CDMPCs are electrospun to form nanofibrous membranes and their morphology is 23 studied in relation to the electrospinning process parameters, the degrees of polymerizations of the 24 CDMPCs, and their solution concentrations. Liquid-liquid permeation experiments of a racemic 25 compound, (R,S)-1-(1-naphthyl)ethanol, through the CDMPCs membranes demonstrate preferable 26 permeation of the S-enantiomer. This is supported by theoretical simulations using a molecular 27 docking model that indicate stronger hydrogen bonding and π - π interactions with higher binding 28 energy between CDMPC and the *R*-enantiomer than the *S*-enantiomer.

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³⁰ Keywords: Cellulose tris-(3,5-dimethyl phenyl carbamate), Electrospinning, Nanofiber,

³¹ Enantioselective membrane, Chiral resolution, Molecular docking simulation

33 Introduction

34 Biologically active compounds, such as drugs, agrochemicals, food additives, etc. often contain 35 chiral structures in their molecules. Since their physiological properties usually depend on this 36 chirality, great efforts have been made to produce chirally pure compounds. In general, there are 37 two typical approaches (Kaya et al. 2023): one is asymmetric synthesis and the other is chiral 38 resolution, in most cases, by High Performance Liquid Chromatography (HPLC) (Okamoto and 39 Ikai 2008; Shen and Okamoto 2016). The former uses chiral sources such as chiral catalysts and 40 enzymes that are often specific for each desired chiral molecule and is, thus, not a versatile 41 approach for various chiral compounds despite its potential for large-scale production. On the 42 other hand, the latter is more versatile for producing various chiral compounds although it is 43 unsuitable for large-scale production due to its discontinuous batch process. We note that the chiral 44 chemicals market size is expected to increase by 5.89 billion US\$ from 2020 to 2025 according to 45 TechNavio Ltd., UK ("Chiral Chemicals Market by Application and Geography - Forecast and 46 Analysis 2021-2025" https://www.technavio.com/report/chiral-chemicals-market-industry-47 analysis. Accessed on February 16, 2023). Given this rapid expansion, there is urgent need for 48 novel strategies that enable large-scale continuous chiral resolution based on a deeper 49 understanding of the mechanism.

50 Chiral resolution via enantioselective membrane filtration, which is one of the promising 51 strategies for large-scale continuous processing, has been reported since 1980s (Liu et al. 2021; 52 Vedovello et al. 2022). Various enantioselective membranes were prepared from natural chiral 53 polymers (e.g., polypeptides and polysaccharides) and their derivatives. Aiming to improve the 54 interaction between the membranes and chiral molecules, porous materials with large specific 55 surface area (SSA) such as metal organic frameworks (MOFs) (Das et al. 2018; Gong et al. 2022) 56 and covalent organic frameworks (COFs) (Wang et al. 2020; Zhuo et al. 2020) were recently 57 utilized as ingredients of enantioselective membranes. Electrospun nanofibrous textile is another 58 potential material of enantioselective membranes with large SSA and mechanical integrity. For 59 example, chemically and/or physically functionalized achiral synthetic polymers such as 60 poly(ethylene terephthalate) (Yoshimatsu et al. 2008) and polysulfone (Mizushima et al. 2012; 61 Sueyoshi et al. 2012; Yoshikawa et al. 2007) with various chiral selectors (CSs) were electrospun 62 to form nanofibrous membranes and their potential for chiral resolutions have been reported. 63 Electrospun membranes made of polysaccharides such as cellulose triacetate (Kawasaki and 64 Yoshikawa 2013) and chitin (Shiomi and Yoshikawa 2013; Shiomi and Yoshikawa 2016) and 65 their derivatives also demonstrated chiral resolution properties. Although these previous and 66 cutting-edge studies ensure a promising outlook of the membrane-based chiral resolutions, there 67 are still many hurdles to overcome for efficient chiral resolutions as has been achieved by HPLC. 68 In addition, the detailed mechanism of chiral discrimination at a molecular level is still unclear.

Polysaccharides and their derivatives have been widely used as CSs in chiral resolutions (Okamoto and Yashima 1998; Peluso et al. 2020). Among them, cellulose and amylose derivatives notably phenylcarbamates and esters are known as the most popular CSs when immobilized on silica gels, so-called chiral stationary phases (CSPs), that are packed in the columns for HPLC. 73 Despite their discrimination properties for a wide range of chiral molecules, these polysaccharide 74 based CSs always need a kind of scaffold to be immobilized, e.g., silica gels in the case of CSPs in 75 HPLC columns. Recently, we prepared a self-standing nanofibrous membrane made of cellulose 76 tris(3,5-dimethylphenylcarbamate) (CDMPC), one of the most versatile CSs used in chiral HPLC 77 columns, by electrospinning and demonstrated their enantioselective permeation property (Otsuka 78 et al. 2021). The great advantage of electrospinning is that one can prepare the enantioselective 79 membrane consisting purely of the CS, in this case CDMPC, as the spinning polymer. In addition, 80 thanks to their simple fabrication process, the morphology of electrospun membranes can be 81 controlled. Indeed, important properties of the nanofibrous membranes such as the fiber diameter, 82 membrane thickness, porosity, SSA etc. can be controlled by adjusting the process parameters 83 (e.g., applied voltage, solution feed rate, and tip-to-collector distance) (Thompson et al. 2007) as 84 well as the properties of the spinning polymer (e.g. degree of polymerization (DP), solvent, and 85 concentration) (Fong et al. 1999; Greiner and Wendorff 2007).

86 In this study, CDMPCs having different DPs are synthesized from hardwood-derived cellulose 87 fiber samples with different fiber length and width. The CDMPCs are electrospun and the 88 morphologies of the products are investigated with variation of the process parameters such as the 89 applied voltage and the solution feed rate, as well as the DPs and the concentrations of the 90 CDMPCs. Enantioselective permeation of (R,S)-1-(1-naphthyl)-ethanol through the electrospun 91 membranes is characterized by liquid-liquid permeation experiments. Molecular binding free 92 energies between CDMPC and R-/S-1-(1-naphthyl)ethanol are theoretically calculated by a 93 molecular docking method and compared to the experimental results of the enantioselective 94 permeation.

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96

97 Experimental

98 Materials

99 TECHNOCEL[®]-10, -200, and -1000 cellulose fiber samples were gifted from CFF GmbH & Co. 100 and used after drying under vacuum at 65 °C overnight. 3,5-Dimethyl phenyl isocyanate (99%) 101 was purchased from Alfa Aesar Co. and used as received. (*R*,*S*)-1-(1-naphthyl)ethanol (\geq 99.0%), 102 *n*-hexane for HPLC (\geq 95%), 2-propanol gradient grade for liquid chromatography (\geq 99.9%), and 103 N.N-dimethylacetamide (DMAc) (99%) were purchased from Sigma-Aldrich Co. and used as 104 received. Acetone (\geq 99.8%), dimethylformamide (DMF), tetrahydrofuran (THF), and ethanol 105 were purchased from Biosolve Chimie Co. and used as received. Methanol (\geq 99%) was purchased 106 from Carlo Erba Co. and used as received.

107

108 Instruments

109 Attenuated Total Reflection-Fourier Transform Infrared (ATR-FTIR) spectra were obtained using

110 a PerkinElmer Spectrum Two spectrometer. Proton nuclear magnetic resonance (¹H NMR) spectra

111 were recorded on a Bruker Advance DRX400 (400 MHz) spectrometer. Size Exclusion 112 Chromatography (SEC) was performed with an Agilent Technologies 1260 Infinity Multi Detector 113 Suite GPC/SEC System equipped with a refractive index (RI) detector, a ultraviolet (UV) detector, 114 and a dual-angle (90° and 15°) light scattering (LS) detector, and a set of columns (Shodex 115 Asahipak GF-1G 7B, GF-7M HQ, and GF-310 HQ) operating at 40 °C using DMF containing 0.01 116 M LiCl as an eluent at a flow rate of 0.6 mL/min. A Wyatt Optilab rEx differential refractive index 117 detector was used to determine dn/dc values. Electrospinning was performed by a Fuence Esprayer 118 ES-2000S2A. The scanning electron microscope (SEM) images of the specimens coated with a ca. 119 4 nm-thick layer of gold/palladium (Au/Pd) were observed by a FEI QUANTA FEG 250 120 microscope operating at an accelerating voltage of 2.5 kV. High Performance Liquid 121 Chromatography (HPLC) was performed with a Thermo Fisher Scientific UltiMate 3000 HPLC 122 system equipped with a VWD-3100 UV ($\lambda = 270$ nm) detector and a Daicel CHIRALPAK[®] IB N-123 3 (length \times inner diameter: 100 \times 4.6 mm, particle size: 3 μ m) analytical column operating at 124 30 °C using a mixed solvent of *n*-hexane and 2-propanol, i.e. *n*-hexane/2-propanol = 9/1 (v/v), as 125 an eluent at a flow rate of 1.0 mL/min. A Techpap MorFi image analyzer was used to characterize 126 TECHNOCEL cellulose fibers' morphology by image analysis.

127

128 Morphological characterization of TECHNOCEL cellulose fiber samples

0,3 g of each TECHNOCEL fiber sample was dispersed in 1 L of water and characterized with the
MorFi image analyzer. Several thousand fibers were analyzed in order to assess cellulosic fiber
dimensions: average and distribution of fibers lengths and widths. The mean fiber lengths (mean
length-weighted length) were determined as below:

133

$$\sum_{i=1}^{n} (L_i \times L_i) \bigg/ \sum_{i=1}^{n} L_i$$

134 where L_i is the length of the fiber *i*.

135

136 Syntheses of CDMPCs

137 Syntheses of CDMPCs from TECHNOCEL cellulose fiber samples were achieved according to a 138 previously reported method used for microcrystalline cellulose as the starting material (Okamoto 139 et al. 1986) with several modifications. TECHNOCEL-10, -200, and -1000 samples (1.00 g of 140 each) were vigorously stirred in dry pyridine under reflux until the fibers disperse completely 141 without any aggregation: TECHNOCEL-10 and -200 were stirred in 25 mL of pyridine for 12 h, 142 while TECHNOCEL-1000 was stirred in 50 mL of pyridine for 24 h. After cooling down the 143 suspensions to room temperature, an excess of 3,5-dimethylphenyl isocyanate (5.00 g, 34.0 mmol) 144 were added dropwise to the suspensions and the mixtures were stirred under reflux for 24 h for the 145 mixture of TECHNOCEL-10 and 48 h for those of TECHNOCEL-200 and -1000. The mixtures 146 were cooled to room temperature, then slowly poured into methanol. The precipitates were 147 collected by filtration, then dissolved in THF and re-precipitated in methanol. Finally, the precipitates collected by filtration were dried in vacuo to obtain CDMPC-10, -200, and -1000 (the
numbers are corresponding to those of the starting TECHNOCEL samples) as white solids (yields:
3.26 g, 3.23 g, and 3.04 g for CDMPC-10, -200, and -1000, respectively). The molecular weights
and molecular weight distributions were determined by SEC analysis and summarized in Table 1.
The degree of substitution (DS) of the CDMPCs were calculated from the ¹H NMR spectra
according to the following equation:

154
$$DS = \frac{\sum H_{AGU} \cdot \int H_{NH}}{\int H_{AGU} \cdot \sum H_{NH}}$$

where $\sum H_{AGU}$ is 7 protons in the anhydroglucose unit (AGU), $\sum H_{NH}$ is 1 proton of N-*H* in the urethane group, $\int H_{AGU}$ is integral of the 7 protons in the AGU, and $\int H_{NH}$ is integral of the 1 proton of N-*H* in the urethane group.

158

159 Electrospinning

160 The electrospinnings of the CDMPCs (0.82 g for all the samples) dissolved in a mixed solvent 161 system, acetone/DMF = 3/2 (v/v), with various concentrations (2-12 wt%) were performed at room 162 temperature (ca. 25 °C) and humidity (ca. 30%). A metallic electrode plate (20 cm × 20 cm square) 163 covered with aluminum foil was placed at 15 cm below the tip of the needle (Nordson stainless 164 steel tips 18 gauge; inner diameter = 0.84 mm, outer diameter = 1.27 mm). A high voltage of 15 165 kV (unless stated otherwise) was applied between the needle and the electrode plate while the 166 sample solutions were passed with an appropriate solution feed rate 10 μ L/min (unless stated 167 otherwise) from the needle to the collector. The electrode plate was continuously moved as its 168 center draws a 5 cm \times 5 cm square controlled by a computer program so that the fibers are 169 electrospun evenly over the entire surface of the aluminum foil.

170

171 Morphological characterization of the electrospun products

172 The morphology of the electrospun products was characterized by SEM observation. The 173 diameters of the electrospun fibers in the membranes and their distributions were statistically 174 analyzed utilizing more than 100 randomly selected fibers from the SEM images using ImageJ 175 open-source software. It should be noted that several SEM images were used for the statistical 176 analysis when there was a small number of the fibers in one image. The thicknesses of the 177 membranes were measured using a Mitutoyo IP65 Digital Micrometer. The specific surface areas 178 (SSAs) of the CDMPCs membranes were determined by measuring adsorption-desorption 179 isotherms of nitrogen at 77 K using a Micromeritics ASAP 2010 volumetric apparatus as described 180 in the literature (Fumagalli et al. 2013).

181

182 Chiral separation

183 Chiral separation of (R,S)-1-(1-naphthyl)-ethanol as a model racemic compound was performed 184 via liquid-liquid permeation (Otsuka et al. 2021) as detailed below. An electrospun CDMPC 185 membrane collected on an aluminum foil was cut into a small piece (ca. 3 cm × 3 cm square) and 186 the membrane was carefully peeled off from the aluminum foil using tweezers. The peeled 187 membrane was sandwiched between two Whatman® polytetrafluoroethylene (PTFE) membrane 188 filters (pore size: 1 µm, diameter: 47 mm) as a support of the membrane to compose the final 189 CDMPC membrane system. The CDMPC membrane system was arranged between a pair of 15 190 mm unjacketed "Side-Bi-Side" glass cells (PermeGear Inc.) equipped with magnetic stir bars in 191 each cell. A mixed solvent of *n*-hexane and 2-propanol) with the volume ratio of 9 to 1 (*n*-192 hexane/2-propanol = 9/1 (v/v)) was used as eluent for the following permeation experiments (cf. 193 Figure 8). A 5 mL solution of (R,S)-1-(1-naphthyl)-ethanol in the eluent (2 g/L) was placed in the 194 left-side cell and a 5 mL of the eluent was placed in the right-side cell. The solutions in both cells 195 were stirred and a 150 μ L of the solution in the right-side cell was sampled every 1 minute for the 196 HPLC analysis. The sample solutions containing permeated R- and S-1-(1-naphthyl)-ethanol from 197 the right-side cell were analyzed by the HPLC equipped with a CDMPC packed column (Daicel 198 CHIRALPAK® IB N-3). The enantiomeric excess (e.e.) values (%) of the samples were 199 determined by comparing the two independent peak areas of the S-enantiomer and the R-200 enantiomer from the HPLC chromatograms according to the following equation:

201
$$e.e.(\%) = \frac{A_{\rm S} - A_{\rm R}}{A_{\rm S} + A_{\rm R}} \times 100$$

where $A_{\rm S}$ and $A_{\rm R}$ are the peak areas of the *S*-enantiomer and the *R*-enantiomer in the chromatogram, respectively.

204

205 Water contact angle (WCA) measurement

The WCAs of the CDMPCs membranes were examined using an I.T. Concept Tracker tensiometer at room temperature. A 10 μ L of deionized water was dropped on each membrane fixed on a glass slide and the contact angle was measured when the angle became stable after 15 sec. Measurements were made five times for each membrane and the mean angle was determined as the WCA for each sample.

211

212 Molecular construction and docking simulation

213 ChemBioDraw Ultra version 12.0 (PerkinElmer Inc.) was used to construct the 3D structures of 214 CDMPC, R-1-(1-naphthyl)ethanol, and S-1-(1-naphthyl)ethanol. The structures were then energy 215 minimized using the MM2 energy minimization algorithm of ChemBio3D. AutoDock version 4.2 216 (Scripps Research Institute), PyMOL version 1.5.7 (Schrödinger, Inc.), and BIOVIA Discovery 217 studio visualizer 4.5 (3DEXPERIENCE) open-source software were used for docking simulations. 218 AutoDock Tools (ADT) 1.5.6. was employed to process the structures of CDMPC, R-1-(1-219 naphthyl)ethanol, and S-1-(1-naphthyl)ethanol prior to docking. For CDMPC, the Kollman and 220 Gasteiger charges were computed, while for R- and S-1-(1-naphthyl)ethanol, Gasteiger charges 221 and rotatable bonds were assigned. The structures of R- and S-1-(1-naphthyl)ethanol (Ligands) 222 were treated as flexible while the structure of CDMPC was kept rigid in the docking protocol. The 223 AutoGrid program was employed to generate 3D affinity grid fields. A grid of size ca. 80×70×40 224 $Å^3$ with 0.375 Å spacing was used for docking. The default settings were used for all other 225 parameters. CDMPC-Ligands interactions and scoring functions were used to choose the docked 226 structures and for further analysis. Results differing by less than 2 Å in a positional all atom-based 227 root mean-square deviation (RMSD) were clustered together. The average binding free energy was 228 calculated according to the following equation (Ke et al. 2021; Luo et al. 2022):

$$E = \sum_{i=1}^{n} (E_i \times X_i)$$

where *E* is the average binding free energy, *n* is the number of conformational clusters, E_i is the binding free energy of this cluster conformation, X_i is percentage frequency of this cluster conformation. The greater negative values of the binding energy reflect the greater stability of the enantiomer–CDMPC binding.

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235

236 Results and discussion

237 Synthesis of CDMPCs having different DPs

238 A variety of cellulose triphenylcarbamate derivatives were synthesized from commercially 239 available microcrystalline cellulose and their properties as CSs for enantioseparation have been 240 widely studied. In most cases, the CSs were immobilized on silica gels to be packed in HPLC 241 columns and used as CSPs. Recently, we discovered a new potential of a representative CS, 242 CDMPC, as enantioselective membranes in the form of electrospun nonwoven textiles. The 243 molecular weight is one of the important parameters governing the morphology of the membranes, 244 which must be investigated in relation to the electrospinning process parameters to improve the 245 quality of the membranes. For this purpose, CDMPCs having different DPs were synthesized from 246 hardwood derived cellulose fiber samples with different fiber lengths and widths, namely 247 TECHNOCEL-10, -200, and -1000. First, the TECHNOCEL samples were characterized by 248 microscopy and the MorFi image analyzer. Figure 1 shows optical microscope and SEM images of 249 the TECHNOCEL samples. Obviously, the fiber lengths increase with the numerical order of the 250 TECHNOCEL samples, while the fiber widths are almost same. Indeed, the calculated mean fiber 251 lengths of TECHNOCEL-10, -200, and -1000 were 305.0 µm, 398.5 µm, and 617.5 µm, 252 respectively, and the distributions (%) of short fibers decreased, while those of long fibers 253 increased with the numerical order of the TECHNOCEL samples as shown in the top of Figure 2. 254 On the other hand, the calculated mean fiber widths are around 20 µm for all the TECHNOCEL 255 samples and the distributions of the fiber widths were almost same as shown in the bottom of 256 Figure 2.





258 Figure 1. Optical microscope (OM) images (top) and SEM images (bottom) of TECHNOCEL-

259 1000 (a and d), -200 (b and e), and -10 (c and d).

260



261

262

Figure 2. The mean fiber lengths and fiber lengths distribution (top) and the fiber widths and fiber
widths distributions (bottom) of TECHNOCEL-10, -200, and -1000 determined by the MorFi
analyses.

266

Second, the TECHNOCEL samples were functionalized with 3,5-dimethylphenyl isocyanate in pyridine to synthesize the CDMPCs using a reported method (Okamoto et al. 1986) for the functionalization of microcrystalline cellulose with several modifications (Scheme 1). For successful functionalization, it was important to pre-disperse the TECHNOCEL samples in pyridine by vigorously stirring them under reflux before starting the reactions in order to avoid 272 aggregation of the cellulose fibers that hinder the reactions. As the reactions proceeded, the 273 mixtures became homogeneous solutions and the products were isolated by re-precipitations of the 274 mixtures from THF to methanol. Figure 2 shows ATR-FTIR spectra of the starting cellulose 275 samples (TECHNOCEL-10, -200, and -1000) and the corresponding functionalized products 276 (namely CDMPC-10, -200, and -1000). In the spectra of the TECHNOCEL samples (the spectra 277 shown in black), typical broad absorption bands corresponding to the O-H stretching vibration of 278 cellulose were observed in 3600-3000 cm⁻¹ region. On the other hand, these broad absorption 279 bands of the hydroxyl groups of cellulose did not exist in the spectra of the functionalized products 280 (the spectra shown in red), while absorption bands corresponding to the N-H stretching vibration 281 around 3475 cm⁻¹, the C=O stretching vibration around 1715 cm⁻¹, and the C-C stretching 282 vibration in the aromatic ring around 1590 cm⁻¹, 1520 cm⁻¹, and 1445 cm⁻¹ were clearly observed. 283 ¹H NMR spectra of the products shown in Figure 4 demonstrate characteristic signals of urethane 284 N-H protons (8.6-8.0 ppm), aromatic protons (7.4–6.2 ppm), cellulose backbone protons (5.2–3.4 285 ppm), and aryl-methyl protons (2.5–1.7 ppm) corresponding to the chemical structure of CDMPC. 286 The DS values calculated from the peak integrations of the N-H protons and the cellulose 287 backbone protons were almost 3 (the calculated DS values for CDMPC-10, -200, and -1000 were 288 3.08, 3.15, and 3.01), which confirms quantitative substitutions of the hydroxyl groups on the 289 starting cellulose by 3,5-dimethylphenyl carbamate groups. These results are in line with that 290 reported in literature for the CDMPCs synthesized from microcrystalline cellulose (Bui et al. 2023; 291 Otsuka et al. 2021; Weng et al. 2013). Absolute molecular weights of the CDMPCs were measured 292 by SEC equipped with a dual-angle (15° and 90°) LS detector. The SEC traces (intensity of LS at 293 15° vs. elution time) of the CDMPCs and a CDMPC synthesized from microcrystalline cellulose 294 (CDMPC-MCC) previously reported by us (Otsuka et al. 2021) for comparison are shown in 295 Figure 5. The number-average molecular weight (M_n) , the weight-average molecular weight (M_w) , 296 the molecular weight dispersity ($D_{\rm M} = M_{\rm w}/M_{\rm n}$), and the DP are summarized in Table 1. All the 297 CDMPCs synthesized from the TECHNOCELs have higher molecular weights than those of 298 CDMPC-MCC and different from each other, i.e., the molecular weights increase in the order of 299 CDMPC-MCC, -10, -200, and -1000. Consequently, the CDMPCs having different DPs were 300 successfully obtained from the TECHNOCEL cellulose fiber samples.





Scheme 1. Synthesis of the CDMPCs from TECHNOCEL hardwood cellulose fiber samples.

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- 304



Figure 3. ATR-FTIR spectra of the starting cellulose samples: the spectra (a), (b), and (c) shown
in black are respectively TECHNOCEL-10, -200, and -1000, and the products after
functionalizations: the spectra (d), (e), and (f) shown in red are respectively CDMPC-10, -200, and
-1000.





312 Figure 4. ¹H NMR spectra of (a) CDMPC-10, (b) CDMPC-200, and (c) CDMPC-1000 in acetone-

- d_6 (solvent residual signals: *H₂O and **acetone).





Figure 5. SEC traces of (a) CDMPC synthesized from MCC (CDMPC-MCC) shown with the dotline, (b) CDMPC-10 shown with the green line, (c) CDMPC-200 shown with the red line, and (d)
CDMPC-1000 shown with the blue line.

321 **Table 1**. Molecular property of the CDMPCs

Starting cellulose	CDMPCs	M _n (g/mol)	$M_{\rm w}({ m g/mol})$	$\mathbf{D}_{\mathrm{M}^{a}}$	DP ^b
MCC (Avicel PH-101)	CDMPC-MCC ^c	87,400	146,000	1.67	242
TECHNOCEL-10	CDMPC-10	399,000	657,000	1.65	1,090
TECHNOCEL-200	CDMPC-200	442,000	895,000	2.02	1,480
TECHNOCEL-1000	CDMPC-1000	609,000	1,170,000	1.93	1,940

322 ${}^{a}\mathcal{D}_{M} = M_{w}/M_{n}$. b DP = $M_{w}/603.67$: molar mass of the monosaccharide unit of CDMPC (DS = 3).

323 ^c This polymer was previously reported by the authors (Otsuka et al. 2021).

324

325 Electrospinning

326 The obtained CDMPCs from TECHNOCELs were soluble in several organic solvents that are 327 good solvents of CDMPC-MCC such as acetone, THF, DMF, and DMAc regardless of their DPs. 328 For the successful electrospinning of CDMPC-MCC, it was important to adjust the vapor pressure 329 of the solution by mixing higher volatile solvents (acetone or THF) and lower volatile solvents 330 (DMF or DMAc) in order to stabilize the jet of the solution on the tip of the needle-electrode. 331 Indeed, electrospinning of the solution of CDMPC-MCC in a mixture of higher volatile acetone 332 and lower volatile DMAc with the ratio of 1/1 (v/v) gave a stable electrospinning process to form 333 self-standing nanofibrous membranes. The same solvent system (acetone/DMAc = 1/1 (v/v)), 334 however, did not give good electrospinning condition for the CDMPCs having higher DPs 335 (CDMPC-200 and -1000), i.e. the solvent was not fully evaporated during the elecrospinning 336 process and the collected fibers on the aluminium foil seemed like melted off. Therefore, to 337 improve the volatility, DMAc (bp 165 °C) was replaced by slightly more volatile DMF (bp 338 153 °C) and the volume ratio of higher volatile acetone (bp 56 °C) was increased from 50% to 339 60%, i.e., acetone/DMF = 3/2 (v/v). This mixed solvent was adopted as the solvent system for all 340 the electrospinning in this study. Effects of technical parameters such as polymer solution feed rate 341 and applied voltage on the morphology of the electrospun products were investigated as described 342 in the Electronic Supplementary Material.

343 The morphology of electrospun products is strongly affected by molecular weight (or 344 equivalently, DP) and concentration of polymer that govern the viscosity of the polymer solution. 345 Therefore, various solutions of the CDMPCs having different DPs and concentrations were 346 electrospun with a constant solution feed rate (10 μ L/min) and applied voltage (15 kV), and their 347 morphology was characterized by SEM observation. First, CDMPC-10 solutions with the 348 concentrations varied from 2 to 12 wt% in steps of 2% were prepared for the electrospinning. SEM 349 images of the obtained products and the histograms of the constituent fiber diameter distributions 350 determined by statistical analysis of the SEM images are shown in Figure 4. From the solution 351 with the lowest concentration of 2 wt%, fibers coexisting with spherical beads, so-called "bead-on-352 string" fibers, were obtained (Figure 6a), suggesting that the viscosity and/or surface tension of the 353 solution at this concentration is insufficient against the applied electrostatic force. The increase in 354 polymer concentration to 4 wt% and above led to formations of continuous fibers as shown in

355 Figure 6b-f. As widely observed in electorspinning of polymer solutions (Ahmadi-Nohadani et al. 356 2022; Lee et al. 2018; Motamedi et al. 2017), increasing the concentration tended to an increase in 357 mean fiber diameter (MD) from 238 nm (4 wt%) to 554 nm (12 wt%). This can be explained by 358 increase in the viscosity with increase in the solution concentration, i.e., the higher the 359 concentration, the higher the entanglement of the polymer chains, reading them more resistant to 360 the elongation force of the electric field. At the same time, the fiber diameter distributions 361 exhibited a broadening with increasing the concentration, i.e., the standard deviation (SD) value 362 increased from 54 nm (4 wt%) to 137 nm (12 wt%) as shown in Figure 6h-l. This is probably 363 because the electrospinning technical parameters set for the process, such as the distance between 364 the electrodes, the solution feed rate, and the applied voltage kept at constant values were not 365 optimal to allow stable stretching of the polymer solution at higher concentrations. This is 366 especially notable at 12 wt% that shows the most broadened fiber diameter distribution (Figure 6). 367 It was not possible to electrospin the solution of CDMPC-10 with the concentration beyond 12 368 wt% due to coagulation of the polymer on the tip of the needle-electrode. The same trend between 369 the polymer concentration and the fiber morphology was observed for CDMPC-200 and CDMPC-370 1000 as shown in Figure S3 and S4 (in the Electronic Supplementary Material). For all the 371 CDMPCs, the MDs tended to increase with increasing the solution concentrations. The largest SDs 372 were observed at the maximum polymer solution concentrations (12 wt% for CDMPC-10, 8 wt% 373 for CDMPC-200, and 4 wt% for CDMPC-1000) above which the polymers were not 374 electrospinnable due to coagulations of the polymers. It was observed that the maximum 375 concentration decreases as the DP increases as shown in Figure 7. This can be explained by the 376 increase in the viscosity with the increase in the DP, i.e., the higher the DP the more entangled the 377 molecular chains are. In addition, at the same concentration, the MD of the CDMPC having higher 378 DP is always larger compared to the MD with lower DP. For instance, at 4 wt%, the largest MD 379 (993 nm) was observed with CDMPC-1000 (DP = 1,940), followed by the middle MD (539 nm) 380 with CDMPC-200 (DP = 1,480), and the smallest MD (238 nm) with CDMPC-10 (DP = 1,090).

381 Through the electrospinnings described above, a series of nonwoven nanofibrous membranes 382 consisting of the CDMPCs were formed on aluminum foils that covered the electrode plate. In this 383 study, the total mass of the CDMPCs used for 1 electrospinning process was kept constant (0.82 g) 384 regardless of their solution concentrations. As the morphologies of the electrospun fibers (e.g., 385 diameter, density, and porosity) are different from each other, the thicknesses of the obtained 386 membranes are also different. For this reason, it was not possible to peel off some of the 387 membranes from the aluminum foils due to their thin thickness. The electrospun membranes from 388 the solutions of CDMPC-10 (8, 10, and 12 wt%) and CDMPC-200 (6 and 8 wt%) were 389 successfully peeled off from the aluminum foils. These self-standing membranes (Membrane 1-5 390 listed in Table 2) were used for the following characterization of enantioselective permeation.



391

Figure 6. SEM images of the electospun products obtained from the CDMPC-10 solutions in acetone/DMF = 3/2 (v/v) with various concentrations (a-f) and histograms of diameter distributions of the fibers (g-l) determined from the SEM images. *MD: mean diameter. **SD: standard deviation.





Figure 7. The mean fiber diameters with the standard deviations of the electrospun fibers obtained
from CDMPC-10 (the blue bars), CDMPC-200 (the green bars), and CDMPC-1000 (the red bars)
solutions with different concentrations.

Membrane name	Spinning solution	Thickness (nm)	SSA ^a (m ² /g)	WCA (deg)
Membrane-1	CDMPC-10 (8 wt%)	134	6.8	109.4
Membrane-2	CDMPC-10 (10 wt%)	116	6.0	120.4
Membrane-3	CDMPC-10 (12 wt%)	98	4.7	120.2
Membrane-4	CDMPC-200 (6 wt%)	104	4.1	118.8
Membrane-5	CDMPC-200 (8 wt%)	101	4.2	123.9

403 **Table 2**. Physical properties of the membranes used for the liquid-liquid permeation experiments

^a Specific surface area was calculated by nitrogen adsorption at 77 K using the BET equation
(Brunauer et al. 1938).

406

407 Enantioselective permeation of (*R*,*S*)-1-(1-naphthyl)ethanol through the CDMPCs membranes

408 Previously, we reported the enantioselective permeation of (R,S)-1-(1-naphthyl)ethanol through 409 the electrospun membrane made of CDMPC-MCC (Otsuka et al. 2021). The preferential 410 adsorption of the R-enantiomer into the membrane was a driving force for the preferential 411 permeation of the S-enantiomer through the membrane. Herein, the new electrospun membranes 412 made of the CDMPCs synthesized from dried wood pulp was investigated for their 413 enantioselective permeation properties. Enantioselective permeation properties of the CDMPCs 414 membranes were characterized by liquid-liquid permeations of a racemic mixture, (R,S)-1-(1-415 naphthyl)ethanol, through the CDMPCs membranes that were sandwiched between commercially

416 available PTFE membrane filters as support materials using a pair of "Side-Bi-Side" glass cells as 417 shown in Figure 8. A solution of the racemic mixture in the eluent (n-hexane/2-propanol = 9/1)418 (v/v)) was placed in the left-side cell and the same volume of pure eluent was placed in the right-419 side cell. Under gentle stirring, a portion of the solution in the right-side cell was sampled every 1 420 minute to determine *e.e.* (%) of a preferentially permeated enantiomer by the HPLC analysis. This 421 procedure was performed for all the CDMPCs membranes and their enantioselective permeation 422 properties were investigated based on their e.e. versus permeation time. As expected, the S-423 enantiomer was preferentially permeated through all the CDMPCs membranes by the liquid-liquid 424 permeation. The e.e. values of the S-enantiomer in the right-side cell were plotted against the time 425 and shown in Figure 9a and 9b for the permeations using the membranes made of CDMPC-10 426 (Membrane 1-3) and CDMPC-200 (Membrane 4 and 5), respectively. In case of the permeations 427 through Membrane-2 (red line in Figure 9a) and Membrane-4 (pink line in Figure 9b), the highest 428 e.e. values were observed at 1 min, then the e.e. values were gradually decreased over time. These 429 results are in line with the previous result for the liquid-liquid permeation through the membrane 430 made of CDMPC-MCC. As we previously reported for the CDMPC-MCC membrane, these 431 gradual decreases of the e.e. values from the initial stage indicates that the enantioselective 432 sorption of the R-enantiomer in these CDMPCs membranes reached equilibrium at 1 min or 433 before, then both the *R*- and *S*-enantiomers permeate equally through the membranes, resulting in 434 the gradual decrease of the e.e. values over time. On the other hand, the permeations through 435 Membrane-1 (black line in Figure 9a), Membrane-3 (blue line in Figure 9a), and Membrane-5 436 (green line in Figure 9b) demonstrated different behavior, i.e., the e.e. values gradually increased 437 to the highest values and then decreased. These results probably suggest that the enantioselective 438 sorption of the *R*-enantiomer in these CDMPCs membranes did not reach equilibrium at the initial 439 stage until the time at which the *e.e.* values became maximum. Such a difference in the permeation 440 behavior of the membranes can be attributed to a complex interplay of the parameters, such as 441 thickness, SSA, and surface energy of the membranes as summarized in Table 2. Further study on 442 controlling these parameters is necessary to investigate the sorption capacity of the membranes.



444 445

In addition to the experimental approach described above, theoretical approaches such as molecular modeling is of great importance to elucidate the mechanism of chiral recognition within the CDMPCs membranes. Herein, the energy and geometry of the interactions of CDMPC with *R*-

449	and S-1-(1-naphthyl)ethanol were studied by molecular docking simulations using AutoDock
450	molecular modeling simulation software. Previous studies have shown that the chiral recognition
451	sites of CDMPC exist in the cavities between the sheets formed by the cellulose backbone, which
452	incorporate various levels of chiral information (Adhikari et al. 2023; Kasat et al. 2007; Peluso et
453	al. 2019). Discriminations of chiral molecules originate in the fit between such chiral cavities and
454	the enantiomers that is affected by diverse interactions during the separation process (Scriba
455	2016). The binding free energy (ΔG) which evaluates the thermodynamic stability of the complex
456	of CDMPC and R-/S-1-(1-naphthyl)ethanol was calculated by a semi-empirical binding free
457	energy function in the AutoDock. The results of docking simulations are shown in Figure 10 and
458	the calculated ΔG values are listed in Table 3. The obtained ΔG values for both the R- and S-
459	enantiomers were negative, indicating that the retentions of R - and S -1-(1-naphthyl)ethanol in the
460	cavities of CDMPC are enthalpy driven and spontaneous processes (Li et al. 2010; Yao et al.
461	2017). In addition, the higher negative ΔG value for the <i>R</i> -enantiomer ($\Delta G = -4.732$ kcal/mol) than
462	that for S-enantiomer ($\Delta G = -4.687$ kcal/mol) indicates stronger retention of the R-enantiomer than
463	the S-enantiomer. In Figure 10a, the 3D docking pose of the R -1-(1-naphthyl)ethanol and CDMPC
464	demonstrates that the naphthalene group in the R-enantiomer (shown in green) aligns "in phase"
465	with the phenyl ring in CDMPC. On the other hand, the naphthalene group in the S-enantiomer
466	(shown in pink) aligns slightly out of phase with the phenyl ring in CDMPC as shown in Figure
467	10b. This is supported by the shorter π - π interactions distances between the <i>R</i> -enantiomer and
468	CDMPC as reported in Table 3, confirming that there exist stronger π - π interactions between
469	CDMPC and the <i>R</i> -enantiomer than the <i>S</i> -enantiomer. Furthermore, the distances of the hydrogen
470	bondings formed between the urethane groups of CDMPC and the hydroxyl group of the R -
471	enantiomer (2.05 Å and 2.48 Å as shown in Figure 10c) are shorter than those of the S-enantiomer
472	(2.12 Å and 2.69 Å as shown in Figure 10d), suggesting stronger interaction of CDMPC with the
473	R-enantiomer. These results indicate that the enantioselective permeation of S-1-(1-
474	naphthyl)ethanol through the CDMPCs membranes is based-on a stronger interaction and higher
475	binding energy between the R-enantiomer and CDMPC (the difference in binding energy $ \Delta\Delta G $
476	between the <i>R</i> - and <i>S</i> -enantiomers is 0.046 kcal/mol).



482 Figure 9. Plots of *e.e.* (%) of the preferentially permeated *S*-enantiomer though the electrospun
483 membranes from (a) the solutions of CDMPC-10 and (b) those of CDMPC-200 vs time of the
484 permeation.



Figure 10. The 3D docking pose of enantiomers of (a and c) *R*- and (b and d) *S*-1-(1-488 naphthyl)ethanol with CDMPC.

494 Table 3. Binding free energies and interactions between CDMPC and *R*-/*S*-1-(1-naphthyl)ethanol495 calculated by molecular docking method

Chiral molecule	ΔG (kcal/mol)	ΔΔG ª (kcal/mol)	Number of π–π interactions (distances in Å)	Number of hydrogen bondings (distances in Å)
<i>R</i> -1-(1-naphthyl)ethanol	-4.732	0.046	2 (3.60/4.55)	2 (2.05/2.48)
S-1-(1-naphthyl)ethanol	-4.687	0.040	2 (3.59/4.58)	2 (2.12/2.69)

⁴⁹⁶

^a Absolute value of difference of free binding energy between the *R*- and *S*-enantiomer.

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499 Conclusions

500 In summary, commercially available hardwood cellulose fiber samples having different fiber 501 length (TECHNOCEL-10, -200, and -1000) were successfully functionalized to obtain CDMPCs 502 having different DPs (CDMPC-10, -200, and -1000). The CDMPCs were electrospun with specific 503 parameters (solvent, solution feed rate, applied voltage) to form continuous nanofibers and their 504 nonwoven membranes. The morphology of the fibers and membranes were affected by the DP and 505 the concentration of the CDMPCs, i.e. overall, the mean diameter of the fibers tended to increase 506 with the DP and the concentration. The liquid-liquid permeation of (R,S)-1-(1-naphthyl)ethanol 507 through the five examples of the CDMPCs membranes all demonstrated preferable permeations of 508 the S-enantiomer. The theoretical molecular docking simulations of CDMPC with R- and S-1-(1-509 naphthyl)ethanol indicated the enantioselective permeation is due to better retention of the R-510 enantiomer in the chiral recognition cites of CDMPC with higher binding energy via hydrogen 511 bonding and π - π interactions. These findings are a good step forward toward novel chiral 512 resolution system using electrospun nanofibrous membranes consisting of various CSs already 513 used for chiral HPLC.

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