Rapid Uptake of Pharmaceutical Salbutamol from Aqueous Solutions with Anionic Cellulose Nanofibrils: The Importance of pH and Colloidal Stability in the Interaction with Ionizable Pollutants

Tuula Selkälä[a], Terhi Suopajärvi[a], Juho Antti Sirviö[a], Tero Luukkonen[a], Gabriela S. Lorite[b], Simo Kalliola[c], Mika Sillanpää[c, d], and Henrikki Liimatainen[a, *]

[a] *Fiber and Particle Engineering Research Unit, University of Oulu, P.O. Box 4300, FI-90014, Oulu, Finland*

[b] *Microelectronics Research Unit, University of Oulu, P.O. Box 4500, FI-90014, Oulu, Finland*

[c] *Laboratory of Green Chemistry, LUT Savo Sustainable Technologies, Lappeenranta University of Technology, Sammonkatu 12, FI-50130, Mikkeli, Finland*

[d] *Department of Civil and Environmental Engineering, Florida International University, Miami, FL 33174, USA*

* Corresponding author; Tel: +358505659711. Email: henrikki.liimatainen@oulu.fi

Abstract

Micropollutants escaping conventional wastewater treatment processes pose a threat to biota and the environment. Amongst micropollutants, small and ionizable organic compounds are particularly challenging, since their removal depends significantly on prevailing conditions. In this study, anionic cellulose nanofibrils (CNFs) were shown to perform as promising adsorbents for an ionizable pharmaceutical, salbutamol. The adsorbents were produced from wood cellulose through succinylation pretreatment in urea-LiCl deep eutectic solvent (DES), followed by a nanofibrillation procedure. The impact of pH, contact time, salbutamol

concentration, and adsorbent dose on salbutamol uptake were investigated in batch adsorption studies. Based on the results, the chemical modification of cellulose significantly enhanced the adsorption of salbutamol. The adsorption efficiency was mainly dependent on the charge and colloidal stability of the anionic nanofibril suspension rather than the charge of salbutamol, because the adsorption was considerably improved at pH>7 due to the deprotonation of the cellulose carboxyl groups. The experimental maximum adsorption capacity was 196 mg/g. This study highlights the potential of cellulose nanomaterial adsorbents and the importance of controlling the charge of the adsorbent material when developing solutions for ionizable micropollutant removal.

1 Introduction

Clean water is a prerequisite for a healthy life and a necessity for many industrial processes. Conventional wastewater treatments utilize physical, chemical, and microbiological processes, after which the effluent can be discharged into receiving water bodies or distributed for reuse. However, once the water quality targets set out in the environmental permit have been reached, other types of pollutants may still remain and pass the treatment processes. Micropollutants are synthetic and natural substances that are present in the aquatic environment at trace concentrations (few ng/L to several μg/L) [1]. These include e.g. pharmaceuticals, personal care products, industrial chemicals, pesticides and disinfection byproducts originating from industrial, domestic and hospital effluents, agriculture, livestock, and aquaculture and landfill leachates. Micropollutants are suspected to be capable of causing adverse effects on humans, wildlife, and aquatic ecosystems [2]. The problems with most of

the micropollutants originate from their recalcitrant chemical structure, which means that, instead of decomposing, they slowly accumulate into nature. Some other micropollutants may transform and even be removed during treatments and after extended time, but the challenge lies in the fact that they are continuously introduced into the environment due to widespread use [1].

Amongst micropollutants, polar, ionizable, and non-volatile molecules are often considered the hardest to remove [1,3]. One example is salbutamol (4-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol, CAS 18559-94-9) (Figure 1), an amphoteric compound that can be present as four different species in aquatic solutions, depending on the pH [4]. Being a β_2-adrenoceptor agonist with short-acting bronchodilation and anti-inflammatory effects, it is extensively used in the treatment of asthma [5]. Taking into consideration its widespread use, potential harmful effects [6], and inconsistent removal efficiency in conventional wastewater treatment [6–11], more information is needed regarding the behavior of salbutamol in water and its removal mechanisms under different conditions.
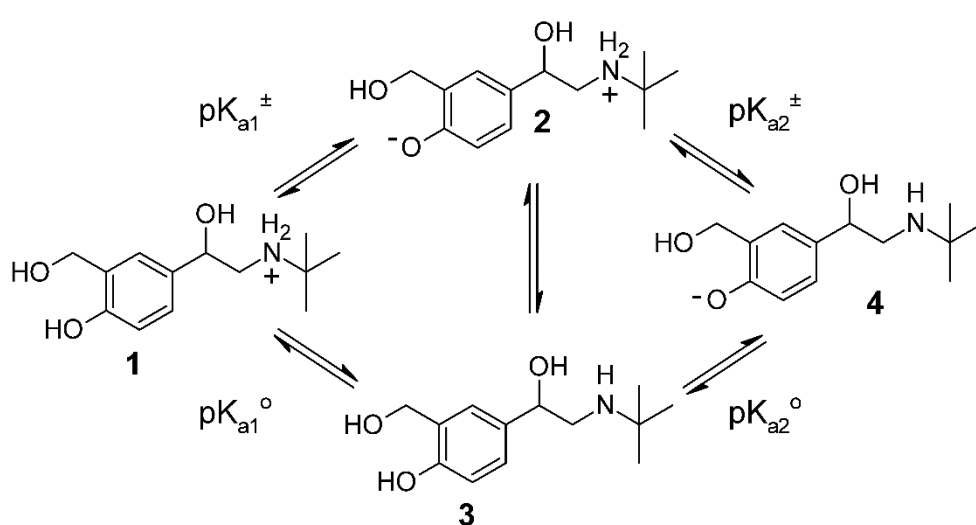
Figure 1. Protonated (**1**), zwitterionic (**2**), neutral (**3**), and deprotonated (**4**) species of salbutamol with microscopic ionization constants $pK_{a1}^{\pm} = 9.22$, $pK_{a2}^{\pm} = 10.22$, $pK_{a1}^{\circ} = 9.60$,

and $pK_{a2}^{°} = 9.84$ [4].

So far, the removal methods of salbutamol have been focused on oxidation [12,13] and photodegradation [14–19] techniques. Despite being effective in degrading contaminants, oxidation processes typically generate intermediates and oxidation products whose stability and toxicity can be higher than that of the micropollutant itself [15]. This drawback of oxidative destruction processes can be avoided by using physical techniques such as adsorption. The usage of bio-based adsorbents, such as cellulose, in the removal of pollutants from water has gained increasing attention during recent years due to their potential wide availability, affordability, high adsorption capacity, regenerability, and lower sludge generation compared to many other processes [20]. In addition, chemical modification can further increase the adsorption capacity of, for instance, cellulosic adsorbents by introducing functional groups [21] or multilayer structures [22] to the material.

Esterification using anhydrides, organic acids, or acid chlorides is an appealing approach to incorporating carboxylic acid functionalities into the cellulose backbone [21]. These reactions are often performed in organic solvents, such as pyridine, and require long reaction times [23,24]. We recently demonstrated a green approach in this area by performing the succinylation reaction on wood cellulose pulp in a deep eutectic solvent (DES) using moderate temperatures (70–90 °C) and reaction times (2 h) [25]. DESs are a new class of solvents that can be prepared from cheap bulk chemicals even at ambient temperatures, and which have showed promising results regarding recyclability and biodegradability [26]. By further disintegrating the chemically modified cellulose fibers into cellulose nanomaterials like cellulose nanofibrils (CNFs), additional properties, such as high reactive surface area and absence of internal diffusion, are introduced to the adsorbent material [27]. The potential of cellulose nanomaterials in water and wastewater treatment is well recognized [28,29].

However, only a few studies so far have reported the adsorption of organic micropollutants onto cellulose nanomaterials [30–33]. More fundamental research focusing on the interaction phenomenon is needed so that the full potential of cellulose nanomaterials in wastewater treatment can be utilized.

In this study, anionic CNFs were produced through succinylation in urea-LiCl DES, followed by disintegration, and subsequently used as adsorbents for aqueous salbutamol. The performance was compared to chemically unmodified CNFs that were produced solely through mechanical disintegration. The effects of solution pH, contact time, initial salbutamol concentration, and adsorbent dose on uptake were examined. In addition, the adsorption isotherms were determined in order to study the removal mechanism. To the best of our knowledge, this is the first time the removal of salbutamol using cellulose nanomaterials has been studied with a focus on wastewater treatment applications.

2 Materials and Methods

2.1 Raw Materials and Chemicals

Commercial softwood dissolving pulp (cellulose 96.2%, hemicelluloses 3.5%, total lignin <0.5%, acetone soluble extractives 0.17%, Domsjö Fabriker AB, Sweden) was received as dry sheets and used as the raw material for the synthesis of the succinylated CNFs. The sheets were disintegrated in deionized water, and the resulting pulp was filtered, washed with technical-grade ethanol, stirred in ethanol for 30 min, and filtered again before drying in an oven at 60 °C. Urea (≥97%, Borealis Biuron®), LiCl (≥99%, Merck pro analysi and VWR AnalaR NORMAPUR® Reag. Ph. Eur.), succinic anhydride (>95%, TCI), and ethanol (96%, VWR) were used in the synthesis.

NaCl (Reag. Ph. Eur., VWR) and 0.5 M NaOH (Oy FF-Chemicals Ab) were used in the carboxyl content determination of the succinylated cellulose fibers.

To characterize the succinylated CNFs by polyelectrolyte titrations, 0.1 M buffer stock solutions (1,000 mL) in the pH range 3–10 were prepared using H_3PO_4 (VWR), NaH_2PO_4 (Sigma), Na_2HPO_4 (Fluka), CH_3COOH (Merck), $CH_3COONa * 3H_2O$ (Oy FF-Chemicals Ab), $NaHCO_3$ (Merck), and Na_2CO_3 (J.T. Baker), all of which were analytical grade. The amount of salts for the preparation of the buffer stock solutions were: pH 10.0 $NaHCO_3$/ Na_2CO_3: 3.016 g (35.99 mmol) $NaHCO_3$ and 6.784 g (64.01 mmol) Na_2CO_3; pH 9.0 $NaHCO_3$/ Na_2CO_3: 7.947 g (94.6 mmol) $NaHCO_3$ and 0.572 g (5.4 mmol) Na_2CO_3; pH 8.0 NaH_2PO_4/ Na_2HPO_4: 1.672 g (13.95 mmol) NaH_2PO_4 and 12.215 g (86.05 mmol) Na_2HPO_4; pH 7.0 NaH_2PO_4/ Na_2HPO_4: 7.42 g (61.9 mmol) NaH_2PO_4 and 5.41 g (38.1 mmol) Na_2HPO_4; pH 5.0 CH_3COOH/ $CH_3COONa * 3H_2O$: 2.16 g (35.9 mmol) CH_3COOH and 8.71 g (64.1 mmol) $CH_3COONa * 3H_2O$; pH 3.0 H_3PO_4/ NaH_2PO_4: 12.0 g (100 mmol) NaH_2PO_4, pH adjusted with dilute H_3PO_4 (9.5–10.5%) and diluted to final volume. Poly(diallyldimethylammonium chloride) (poly-Dadmac, 20% (aq), Aldrich) was used as the titrant.

Salbutamol (98%, Alfa Aesar), 0.1 M HCl, and 0.1 M NaOH (Oy FF-Chemicals Ab) were used in the adsorption experiments.

All of the chemicals were used without purification. Deionized water was used throughout the experiments.

2.2 Succinylation of Cellulose and Disintegration into Nanofibrils

Succinylated celluloses with variable carboxyl contents were synthetized in urea-LiCl DES (Figure 2) using a previously reported procedure [25]. Briefly, dissolving pulp (1.5 g) and succinic anhydride (9.27 g) were reacted in urea-LiCl (molar ratio 5:1) DES for 2–6 h at 70–90 °C. Ethanol (150 mL) was added to the hot stirring mixture to stop the reaction. The mixture was filtered while still hot, and the collected pulp was washed with ethanol (100 mL)

and deionized water (1500 mL). The carboxyl contents of succinylated cellulose derivatives were determined through conductometric titrations [34,35].
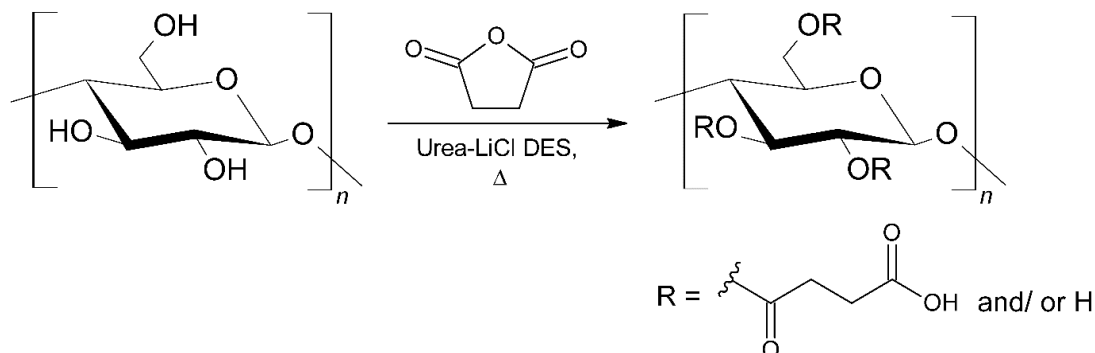
Figure 2. Succinylation of cellulose pulp fibers in urea-LiCl deep eutectic solvent (DES).

The three different reaction conditions applied resulted in an increasing amount of carboxyl content in the succinylated cellulose fibers (samples denoted as SC70, SC80, and SC90, Table 1). The 6 h reaction time was selected for 90 °C reaction to ensure that there is a sufficient difference in the carboxyl contents between the samples. Pristine dissolving pulp was used as a reference material.

Table 1. Reaction Conditions, Carboxyl Contents, and Resulting Nanofibrils of Cellulose Samples.

Sample	Temperature (°C)	Time (h)	Carboxyl content (mmol/g)	Cellulose nanofibril
SC70	70	2	0.34	CNF70
SC80	80	2	0.42	CNF80
SC90	90	6	0.59	CNF90
Dissolving pulp	-	-	0	CNF0

Nanofibrillation of succinylated celluloses was conducted using a microfluidizer (Microfluidics M-110EH-30, USA) with slight modifications to the previously reported procedure (Supplementary Material) [25]. A reference material was prepared from dissolving pulp solely by mechanical disintegration using an ultra-fine friction grinder (Masuko super mass collider MKCA6-2J, Japan) and a microfluidizer (Supplementary Material). The dry matter contents of all CNF suspensions (samples denoted as CNF70, CNF80, CNF90, and CNF0, Table 1) were determined by drying the samples in an oven at 105 °C overnight.

2.3 Characterization of CNFs

2.3.1 Determination of Charge Density by Polyelectrolyte Titration

The measurements were conducted in a buffered medium in the pH range 3–10. The 0.1 M buffer stock solutions were diluted to a concentration of 0.5 mM with deionized water and the pH was adjusted with 0.1 M HCl/NaOH. The pH values of the final buffer solutions were 3.00, 4.98, 6.99, 8.01, 9.03 and 10.01. The CNF samples were diluted to a solids content of 0.1%, after which 1 mL of CNF suspension and 9 mL of appropriate buffer were mixed. The mixture was titrated with poly-Dadmac using a particle charge detector (Mütek PCD 03, USA) while monitoring the charge of the sample.

2.3.2 ζ-Potential Measurements

The samples (50 mL) were prepared by diluting the 5 mg/mL CNF dispersions to 1 mg/mL using water. The pH was adjusted to 9 by adding a few drops of NaOH (0.1 M). The pH was further adjusted by HCl (0.1 and 0.01 M) from pH 9 to 4. Small samples (~0.5 mL) were drawn from the dispersion at desired pH values, and the ζ-potential was measured (Malvern ZetaSizer, England).

2.4 Adsorption Experiments

The effect of pH, stirring time, concentration of salbutamol, and adsorbent dose on salbutamol adsorption were investigated. The parameters for each experiment are shown in Table 2. A stirring time of 4 h was selected for the first experiment (effect of pH) to ensure that the studied system had reached equilibrium before sampling. All experiments were conducted in non-buffered conditions in order to exclude any excess ions that may affect the interaction between the adsorbent and adsorbate. CNF80 was selected for pH, contact time, and salbutamol concentration experiments due to its average charge density and the applied reaction conditions.

Table 2. Parameters for Studying the Effects of pH, Stirring Time, Salbutamol Concentration, and Adsorbent Dose on Salbutamol Adsorption.

	CNF adsorbent	Initial solution pH	Stirring time (min)	Initial salbutamol (mg/L)	Adsorbent dose (mg/L)
pH	CNF80	4–9	240	30	75
Stirring time	CNF80	9	0–1,440	30	75
Initial concentration	CNF80	9	10	5–200	75
Adsorbent dose	All[a]	9	10	30	2.5–100

[a] CNF0, CNF70, CNF80, CNF90

Adsorption studies were performed in 50 mL beakers equipped with magnetic stirring bars. All studies were conducted at room temperature (~21 °C) on a stirring plate adjusted to a 100 rpm stirring rate. The aqueous stock solution of salbutamol (~400 mg/L) was stored at 4 °C between the experiments. Aqueous CNF suspensions were diluted to consistency of

0.2% (~2,000 mg/L) right before use in the adsorption studies. The pH of the 0.2% CNF suspension was adjusted only for the CNF concentration studies (2.5–100 mg/L) and for the lowest salbutamol concentration experiments (5–20 mg/L), so as to keep the pH as constant as possible in the resulting mixtures (non-buffered conditions).

In a typical experiment, a salbutamol solution having the desired concentration was prepared by diluting the stock solution. Then, the pH of the solution was adjusted to the desired value by adding a few drops of dilute HCl or NaOH before reaching the final volume (40 mL) by adding CNF solutions (0.05–2 mL) to the stirred salbutamol solution. The mixture was stirred for a predetermined time, after which it was settled for 30 min. A 10 mL aliquot was taken with a syringe from the center of the mixture (2 cm from the bottom of the beaker) and filtered immediately by a sterile 0.45 μm cellulose acetate syringe filter (VWR, USA). Finally, the pH of the remaining mixture was recorded. The effect of stirring time (10 s–10 min) was also investigated by excluding the 30 min settling time.

The concentration of salbutamol in the filtrate was characterized by UV-vis spectroscopy (Shimadzu UV-1800, Japan) at 276 nm using quartz cuvettes. The absorbance reading was corrected by subtracting the reading at 276 nm obtained for a reference sample, which contained only a corresponding concentration of CNFs and pH as the actual sample. Sampling of the reference samples followed the protocol of the actual samples, as described earlier. The spectrophotometer was calibrated for salbutamol at 276 nm in the range 0–200 mg/L at pH 7 using deionized water as a reference ($R^2 \approx 1$) (Figures S1–S2). Moreover, the spectrum of each sample was recorded at 200–400 nm to monitor the possible changes in the location of the absorbance maximum (Figures S3–S6). The accuracy and daily variation of the absorbance measurements was determined by measuring control solutions of known salbutamol concentration (10 and 20 mg/L, pH 7). The obtained standard deviation was ±0.1 mg/L. Before starting the experiments, the absorbance of a plain salbutamol solution (30

mg/L) was measured before and after filtration to ensure that the syringe filter was not retaining any of the salbutamol.

The amount of adsorbed salbutamol per unit mass of CNF adsorbent at time t, q_t (mg/g) and at equilibrium, q_e (mg/g), were calculated using Equations (1) and (2), respectively:

$$q_t = \frac{(C_0 - C_t)}{m} V \qquad (1)$$

$$q_e = \frac{(C_0 - C_e)}{m} V \qquad (2)$$

where C_0 (mg/L) is the initial concentration, C_t (mg/L) is the concentration at time t (min), and C_e (mg/L) is the equilibrium concentration of salbutamol. V is the volume of the studied solution (L), and m is the dried weight of the CNFs (g). m/V (g/L) is defined as a solid/liquid ratio. The percentage of removed adsorbate from solution was calculated using Equation (3):

$$\%removal = \frac{(C_0 - C_e)}{C_0} \times 100 \qquad (3)$$

2.5 Adsorption Isotherm Models

For the adsorption isotherm studies, the initial salbutamol concentrations of 5–200 mg/L were examined, and CNF80 was used as the adsorbent, with a constant dose of 75 mg/L (Table 2). Higher salbutamol concentrations were not studied since the linearity of the calibration curve started to reach its limits at 200 mg/L, and also because they are unlikely to be encountered in real wastewaters. The adsorption mechanisms were analyzed by fitting Langmuir and Freundlich isotherm models (Supplementary Material).

3 Results and Discussion

3.1 Characteristics of CNFs

The apparent charge densities (Figure 3A) indicate that CNFs can have an attractive electrostatic interaction with salbutamol most efficiently in the pH range of 7–10 (highest

anionic charge density). This could be the optimal for wastewater treatment applications as, for instance, the typical pH of typical municipal wastewaters is 6–8.5. The samples CNF70–CNF90 showed similar behavior throughout the pH range. The anionic charge increased sharply and almost linearly up to pH 7, after which it stabilized. This behavior is explained by the deprotonation of the carboxyl groups (-COOH) as the pH is raised, which increased the anionic charge of the CNFs. In addition, the charges were proportional to the carboxyl group contents in CNFs; i.e., CNF90 had the highest anionic charge in the neutral-alkaline pH region. Similar trends have been observed previously with dicarboxylic acid nanocelluloses [36]. The charge of the unmodified sample CNF0 was close to zero, and it stayed constant throughout the used pH range, as expected, since it did not contain any added carboxyl groups (other than those that resulted from the pulping process).

The ζ-potential results (Figure 3B) are consistent with the apparent charge density measurements, confirming that all samples had an anionic charge through the whole pH range and that the charge increased as the pH became more alkaline. In addition, CNFs formed stable colloidal systems when pH>7, as the aggregation and sedimentation of CNFs caused by the protonation of carboxyl groups were visually observed at pH<7. As expected, the unmodified sample, CNF0, showed low stability. The slightly negative ζ-potential values of CNF0 assumedly originated from the inherent negative charge of the cellulose pulp.
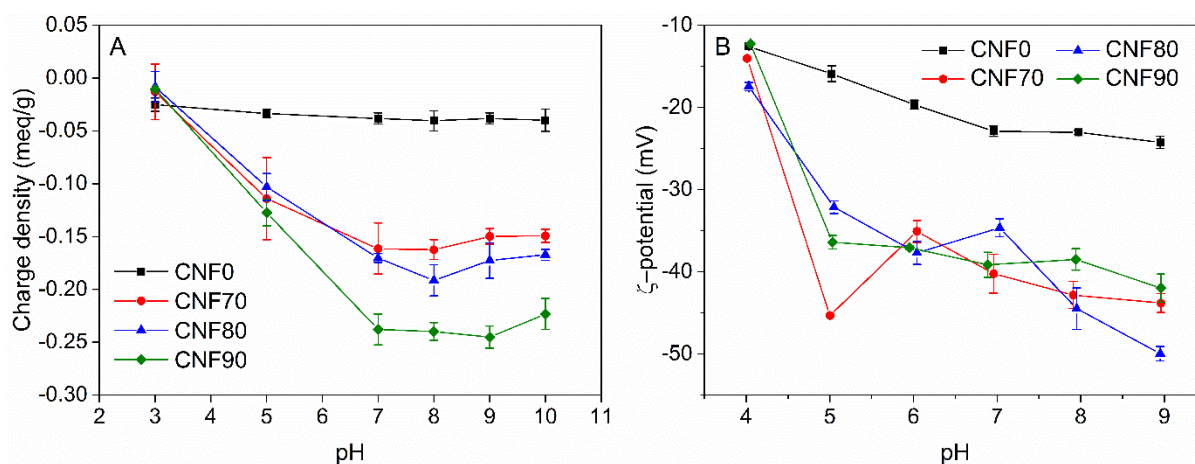
Figure 3. (A) Apparent charge densities of cellulose nanofibrils (0.01% solution) as a function of pH. The data points are averages from two to four titrations. The error bars represent the sample standard deviation or the difference of measured values for more than two or less than three measurements, respectively. (B) The ζ-potential of cellulose nanofibrils (0.1% solution) as a function of pH. The data points are averages of three measurements, and the error bars represent the sample standard deviation.

3.2 Effect of pH and Contact Time on Salbutamol Adsorption

The behavior of CNFs and salbutamol as a function of pH can be predicted by their pK_a values. Typical pK_a values of carboxylic acids are 4–5, which indicates that, at pH values below 4, the carboxyl groups of succinylated celluloses are mainly in protonated form, and above 5 start to be unprotonated, i.e., in anionic form. As shown in Figure 3A, CNF80 reached its maximum anionic charge at pH~8, and a sharp increase in the colloid stability was observed when the pH was above 7 (Figure 3B). Salbutamol, on the other hand, appears solely as protonated species in acidic and neutral solutions (Figure 4A) [14,37]. At higher pH levels, neutral and zwitterionic species are also present, and from pH 9 onwards, the proportion of deprotonated species starts to increase.

Indeed, a notable improvement in the adsorption efficiency was observed as pH was raised above 7, and the maximum adsorption of 101 mg/g, corresponding to 25% removal,

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was reached at pH 8.5 (Figure 4B). These results support the charge density and ζ-potential

measurements, which indicated favorable interaction between salbutamol and adsorbents in

this pH range. The pH of the diluted (0.2%) CNF solutions used in the adsorption studies

were ~7.5, which means that the CNFs were in anionic form (Figure 3A) upon addition.
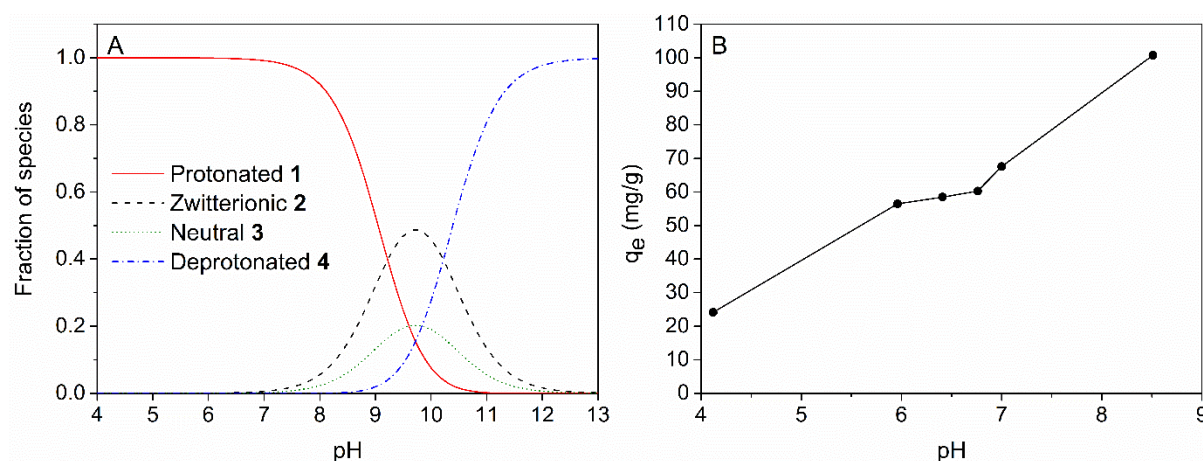
Figure 4. (A) Estimated relative fractions of salbutamol species present at a given pH.

Fractions were calculated using the microscopic ionization constants [4,14,37]. The

numbering refers to the chemical structures presented in Figure 1. (B) Effect of pH on

salbutamol adsorption by succinylated cellulose nanofibrils (stirring time 4 h, salbutamol

concentration 30 mg/L, CNF80 adsorbent dose 75 mg/L). The pH values represent the

readings after 4 h of stirring.

Thus, it can be presumed that the adsorption of salbutamol on CNFs is likely controlled

by the opposite charges of adsorbate and adsorbent, and it is mainly dependent on the charge

of the CNFs, as it closely follows the charge behavior of CNFs (Figure 3A and 3B). On the

other hand, at pH 9, salbutamol is still mainly present as protonated species (53%), and the

zwitterionic (32%) and neutral (13%) species can also interact with cellulose through non-

covalent interactions (Figure 4A). Upon the addition of CNFs, the pH of the mixture shifted

to ~8.5, where the corresponding fractions are 79%, 15%, and 6% for protonated,

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zwitterionic, and neutral salbutamol species, respectively.

The adsorption of salbutamol on CNFs was almost immediate, and the adsorption efficiency settled rapidly to approximately 80 mg/g, corresponding to 20% removal (Figure 5A). Due to the filtration procedure, the shortest reachable contact time was 2 min, and adsorption kinetics were thus not studied further. Although no improvement in the adsorption efficiency occurred by including the 30 min settling time (Figure 5B), it was kept constant in succeeding experiments to keep the sampling conditions intact.
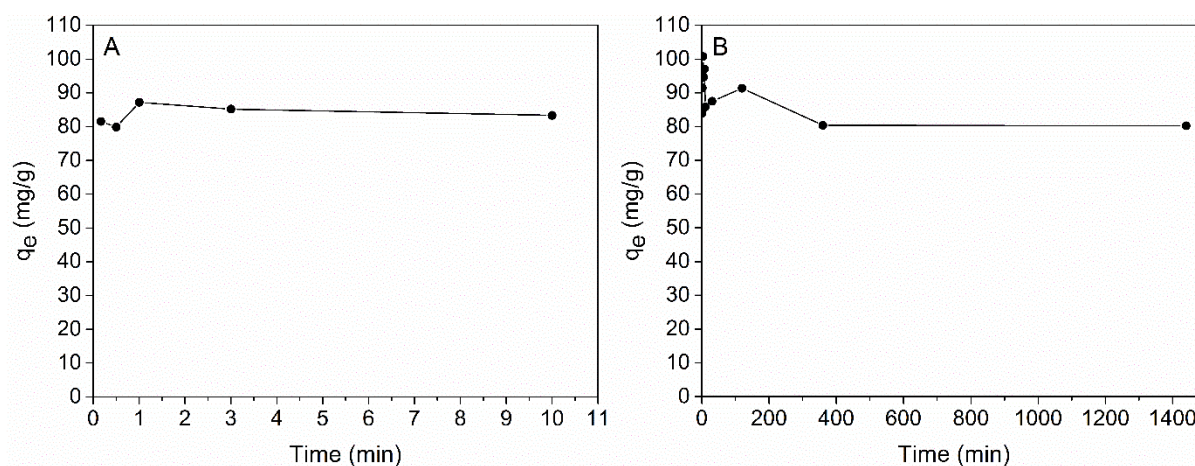
Figure 5. Effect of contact time on salbutamol adsorption by succinylated cellulose nanofibrils (pH 9, salbutamol concentration 30 mg/L, CNF80 adsorbent dose 75 mg/L), (A) with no settling and (B) including an additional 30 min settling.

The CNF samples comprised individual nanofibrils and their bundles as observed via atomic force microscopy (AFM) images (Figure S7). The individualized nanofibrils show a high surface area-to-volume ratio (Figure S7), which means that the need for diffusion inside the adsorbent material is reduced, thus enabling a rapid interaction with salbutamol. Moreover, dilute aqueous suspensions of CNFs mix readily with the water to be treated, which again allows fast interaction with pollutants. Recently, the effect of dry matter content (1.1–1.8% w/w) of anionic CNFs on metal cation sorption was investigated [38]. Lowering

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the dry matter increased the sorption capacity because the interactions between adjacent nanofibrils were weakened. In our case, CNF suspensions having 0.2% (w/w) consistency upon addition were used, implying that the nanofibrils were able to interact with salbutamol immediately.

3.3 Effect of Adsorbent Dose on Salbutamol Adsorption

A significant difference was observed in the salbutamol removal between the unmodified and modified CNFs, as the modified CNFs (CNF70–90) removed up to 27% of salbutamol (CNF dose 100 mg/L), whereas CNF0 adsorbed only 6% (Figure 6A). Increasing the dose of CNF0 did not have an improving effect. This confirmed the assumption that chemical modification is essential to enabling the interaction between salbutamol and CNFs. There was no clear difference in the adsorption efficiency between the modified CNFs (falls within the uncertainty of measurement), possibly due to the too-similar carboxyl group amounts. Adsorption capacities reached their highest values (up to 826–888 mg/g) at the lowest CNF doses (2.5 mg/L) (Figure 6B). As the CNF dose was increased above 25 mg/L, the adsorption capacity settled to approximately 80–100 mg/g, as observed during the kinetic study. An explanation for this is that CNFs are known to form web-like structures through hydrogen bonding as the dry matter content of the CNF suspension is increased, which in turn reduces the amount of available adsorption sites. Thus, the most suitable application mode for CNFs could be as bound on a support material instead of suspension—that is, a continuous process instead of a batch.
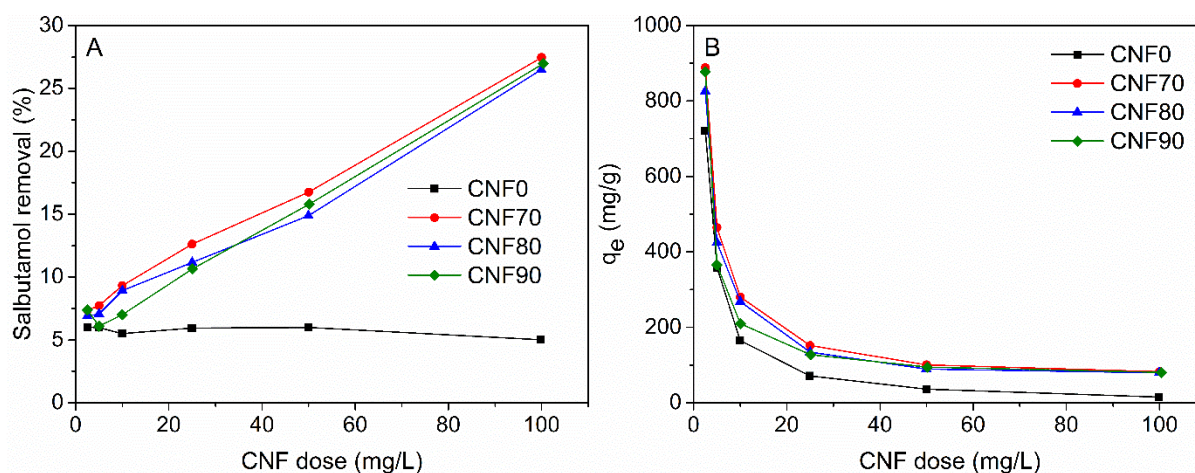
Figure 6. Effect of cellulose nanofibril dose on salbutamol removal (pH 9, stirring time 10 min, salbutamol concentration 30 mg/L), (A) the % removal as a function of adsorbent dose and (B) the amount of salbutamol adsorbed at equilibrium as a function of adsorbent dose.

Although a remarkable difference was observed between modified and unmodified CNFs, the removal efficiency could be improved. CNF80, for instance, had a carboxyl content of 0.42 mmol/g (Table 1), which indicates that ~310 mg/L of CNF80 should be sufficient to adsorb 30 mg/L of salbutamol, assuming 1 mol of carboxyl adsorbs 1 mol of salbutamol. Based on the experimental results 100 mg/L of CNF80 removed 26% of salbutamol, meaning that 310 mg/L would remove 81%. Therefore, it can be presumed that the complete removal of salbutamol could be reached by further increasing the CNF dose, but it would require a different kind of process setup (e.g., CNFs on a solid support). It should be noted, though, that the applied adsorbent doses were significantly lower compared to typical adsorbent studies utilizing cellulose nanomaterials (e.g., 0.5–5 g/L) [24,31–33,39,40].

There are multiple reasons that can explain the observed adsorption efficiency. First, the ammonium cation in salbutamol is sterically hindered due to the adjacent *tert*-butyl group [41]. Second, the free rotation of succinate groups and their closeness to the cellulose backbone can disturb the interaction with salbutamol. It is also possible that the clustering of

the succinate groups in the amorphous regions of cellulose [42] caused steric hindrance, which prevented all available carboxyl groups from interacting with salbutamol.

3.4 Adsorption Isotherms

The experimental adsorption data fitted clearly better with Freundlich isotherm model than Langmuir (R^2 = 0.951 and 0.764, respectively, Table S1). The best-fitting Freundlich isotherm graph for CNF80 is presented in Figure 7. The shape of the isotherm is downward concave and the parameter n is below 1 (0.357), denoting that the adsorption process between salbutamol and CNFs is favorable. The Freundlich isotherm model assumes multilayer adsorption on heterogeneous surfaces. As the succinate groups are likely to be distributed heterogeneously onto the cellulose backbone, it is logical that the CNF adsorbent has different adsorption sites (e.g. hydroxyl groups, succinate groups). The Freundlich isotherm model is not suitable for describing very low or high concentration areas of the equilibrium data, and as a result, it does not describe the saturation behavior of an adsorbent. Therefore, the maximum theoretical adsorption capacity q_m of CNFs cannot be derived. However, the experimental maximum adsorption capacity $q_e(exp)$ was 196 mg/g (corresponds to 0.82 mmol/g) at initial salbutamol concentration of 200 mg/L.
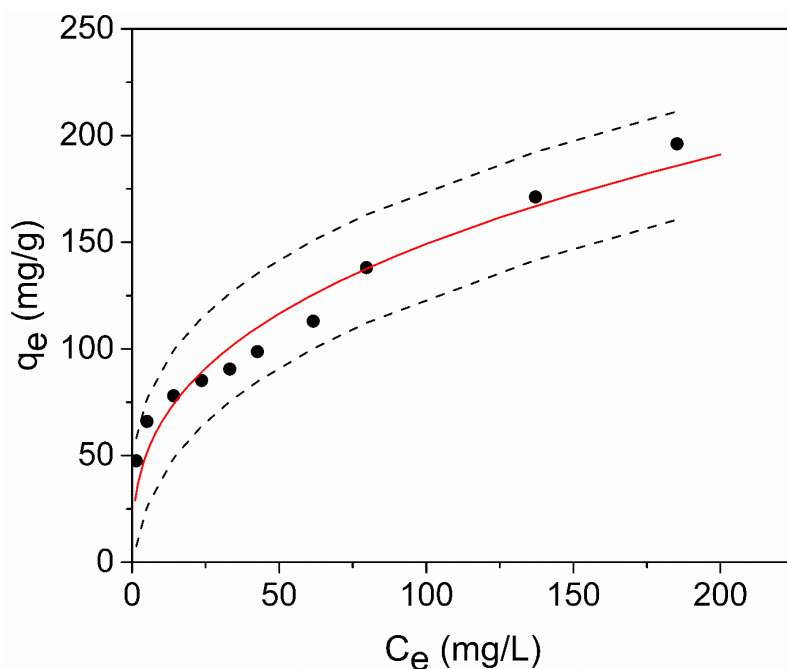
Figure 7. Adsorption isotherm for salbutamol adsorption by succinylated cellulose nanofibrils (pH 9, stirring time 10 min, CNF80 adsorbent dose 75 mg/L). The solid line represents nonlinear regression based on the Freundlich equation, and the dashed lines represent the 95% confidence limits.

There is lack of relevant information about the removal of salbutamol through adsorption in the literature, which limits the comparison of our results to the work of others. The adsorption of salbutamol from ultrapure water onto fresh granular activated carbon (GAC) has been reported to be 80–100% (pH 7, $C_0 = 2$ μg/L, GAC dose 6.7 mg/L) [43]. In the case of a β-blockers atenolol and propranolol, the maximum adsorption capacity of graphene oxide (GhO) has been reported to be 116 mg/g and 67 mg/g, respectively ($C_0 = 10$–150 mg/L, GhO dose 1 g/L) [44]. It should be noted though, that a direct comparison with salbutamol should be avoided due to the different chemical structure of atenolol and propranolol. Overall, the succinylated CNFs seem to be performing well compared with carbon based adsorbents, as the experimental maximum adsorption capacity was 196 mg/g and the results indicated that a complete removal of salbutamol could be reached by further increasing the

CNF dose.

4 Conclusions

The removal of ionizable organic pollutants from water has for long been considered as a demanding task due to their polar and pH dependent nature, which hinders their removal in conventional wastewater treatment processes (e.g. adsorption to sludge) and facilitates their transport to the environment. Based on the results reported herein, the removal of salbutamol through adsorption is controlled mainly by the opposite charges of the adsorbent and adsorbate. Moreover, it is even more important to ensure that the adsorbent nanomaterial carries the maximum charge (in our case anionic), than to maximize the fraction of oppositely charged pollutant species in the water. This finding is advantageous, because it motivates researchers to develop alternative modification methods for adsorbent materials targeted for ionizable micropollutant removal. Especially the inclusion of different types of charged groups and structures to the material would be important, because it would ensure that the adsorbent material remains effective despite the pH or type of charged pollutant species present. This is especially important when treating industrial wastewaters (point source pollution), where the pH levels can differ significantly from municipal wastewater. In addition, our research demonstrated that cellulosic nanomaterials are highly promising also in micropollutant removal as cellulose nanofibrils were shown to rapidly adsorb salbutamol already at low doses. The shortcomings resulting from inter-fibril hydrogen bonding at higher doses could be overcome by developing the process set-up (e.g. fibrils bound in a support material, continuous process).

Acknowledgements

Appendix A. Supplementary Material

Supplementary material associated with this article can be found, in the online version, at

References

[1] Y. Luo, W. Guo, H.H. Ngo, L.D. Nghiem, F.I. Hai, J. Zhang, S. Liang, X.C. Wang, A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment, Sci. Total Environ. 473–474 (2014) 619–641. doi:10.1016/j.scitotenv.2013.12.065.

[2] J.L. Wilkinson, P.S. Hooda, J. Barker, S. Barton, J. Swinden, Ecotoxic pharmaceuticals, personal care products, and other emerging contaminants: A review of environmental, receptor-mediated, developmental, and epigenetic toxicity with discussion of proposed toxicity to humans, Crit. Rev. Environ. Sci. Technol. 46 (2016) 336–381. doi:10.1080/10643389.2015.1096876.

[3] M. Kah, G. Sigmund, F. Xiao, T. Hofmann, Sorption of ionizable and ionic organic compounds to biochar, activated carbon and other carbonaceous materials, Water Res. 124 (2017) 673–692. doi:10.1016/j.watres.2017.07.070.

[4] A.P. Ijzerman, T. Bultsma, H. Timmerman, J. Zaagsma, The ionization of β-adrenoceptor agonists: A method for unravelling ionization schemes, J. Pharm. Pharmacol. 36 (1984) 11–15. doi:10.1111/j.2042-7158.1984.tb02978.x.

[5] K.J. Erb, D.H. Martyres, P. Seither, Antiasthmatic Agents, in: Ullmanns Encycl. Ind. Chem., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2010. doi:10.1002/14356007.a02_453.pub2.

[6] L.H.M.L.M. Santos, M. Gros, S. Rodriguez-Mozaz, C. Delerue-Matos, A. Pena, D. Barceló, M.C.B.S.M. Montenegro, Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals, Sci. Total Environ. 461–462 (2013) 302–316. doi:10.1016/j.scitotenv.2013.04.077.

[7] S. Castiglioni, R. Bagnati, R. Fanelli, F. Pomati, D. Calamari, E. Zuccato, Removal of pharmaceuticals in sewage treatment plants in Italy, Environ. Sci. Technol. 40 (2006) 357–363. doi:10.1021/es050991m.

[8] A. Jelic, M. Gros, A. Ginebreda, R. Cespedes-Sánchez, F. Ventura, M. Petrovic, D. Barcelo, Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment, Water Res. 45 (2011) 1165–1176. doi:10.1016/j.watres.2010.11.010.

[9] O.A.H. Jones, N. Voulvoulis, J.N. Lester, The occurrence and removal of selected pharmaceutical compounds in a sewage treatment works utilising activated sludge treatment, Environ. Pollut. 145 (2007) 738–744. doi:10.1016/j.envpol.2005.08.077.

[10] B. Kasprzyk-Hordern, R.M. Dinsdale, A.J. Guwy, The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters, Water Res. 43 (2009) 363–380. doi:10.1016/j.watres.2008.10.047.

[11] T.A. Ternes, Occurrence of drugs in German sewage treatment plants and rivers, Water Res. 32 (1998) 3245–3260. doi:10.1016/S0043-1354(98)00099-2.

[12] T. Rodríguez-Álvarez, R. Rodil, J.B. Quintana, R. Cela, Reactivity of β-blockers/agonists with aqueous permanganate. Kinetics and transformation products of salbutamol, Water Res. 79 (2015) 48–56. doi:10.1016/j.watres.2015.04.016.

[13] Y. Lan, C. Coetsier, C. Causserand, K. Groenen Serrano, An experimental and modelling study of the electrochemical oxidation of pharmaceuticals using a boron-doped diamond anode, Chem. Eng. J. 333 (2018) 486–494. doi:10.1016/j.cej.2017.09.164.

[14] L.G. Dodson, R.A. Vogt, J. Marks, C. Reichardt, C.E. Crespo-Hernández, Photophysical and photochemical properties of the pharmaceutical compound salbutamol in aqueous solutions, Chemosphere. 83 (2011) 1513–1523. doi:10.1016/j.chemosphere.2011.01.048.

[15] V.A. Sakkas, P. Calza, C. Medana, A.E. Villioti, C. Baiocchi, E. Pelizzetti, T. Albanis, Heterogeneous photocatalytic degradation of the pharmaceutical agent salbutamol in aqueous titanium dioxide suspensions, Appl. Catal. B Environ. 77 (2007) 135–144. doi:10.1016/j.apcatb.2007.07.017.

[16] L. Zhou, Q. Wang, Y. Zhang, Y. Ji, X. Yang, Aquatic photolysis of β2-agonist salbutamol: Kinetics and mechanism studies, Environ. Sci. Pollut. Res. 24 (2017) 5544–5553. doi:10.1007/s11356-016-8207-7.

[17] L. Zhou, M. Sleiman, C. Ferronato, J.-M. Chovelon, P. de Sainte-Claire, C. Richard, Sulfate radical induced degradation of β2-adrenoceptor agonists salbutamol and terbutaline: Phenoxyl radical dependent mechanisms, Water Res. 123 (2017) 715–723. doi:10.1016/j.watres.2017.07.025.

[18] L. Lian, B. Yao, S. Hou, J. Fang, S. Yan, W. Song, Kinetic Study of Hydroxyl and Sulfate Radical-Mediated Oxidation of Pharmaceuticals in Wastewater Effluents, Environ. Sci. Technol. 51 (2017) 2954–2962. doi:10.1021/acs.est.6b05536.

[19] S. Yan, B. Yao, L. Lian, X. Lu, S.A. Snyder, R. Li, W. Song, Development of Fluorescence Surrogates to Predict the Photochemical Transformation of Pharmaceuticals in Wastewater Effluents, Environ. Sci. Technol. 51 (2017) 2738–2747. doi:10.1021/acs.est.6b05251.

[20] A. Bhatnagar, M. Sillanpää, A. Witek-Krowiak, Agricultural waste peels as versatile biomass for water purification – A review, Chem. Eng. J. 270 (2015) 244–271. doi:10.1016/j.cej.2015.01.135.

[21] S. Hokkanen, A. Bhatnagar, M. Sillanpää, A review on modification methods to cellulose-based adsorbents to improve adsorption capacity, Water Res. 91 (2016) 156–173. doi:10.1016/j.watres.2016.01.008.

[22] A. Ottenhall, J. Illergård, M. Ek, Water Purification Using Functionalized Cellulosic Fibers with Nonleaching Bacteria Adsorbing Properties, Environ. Sci. Technol. 51 (2017) 7616–7623. doi:10.1021/acs.est.7b01153.

[23] L.V.A. Gurgel, O.K. Júnior, R.P. de F. Gil, L.F. Gil, Adsorption of Cu(II), Cd(II), and Pb(II) from aqueous single metal solutions by cellulose and mercerized cellulose chemically modified with succinic anhydride, Bioresour. Technol. 99 (2008) 3077–3083. doi:10.1016/j.biortech.2007.05.072.

[24] S. Hokkanen, E. Repo, M. Sillanpää, Removal of heavy metals from aqueous solutions by succinic anhydride modified mercerized nanocellulose, Chem. Eng. J. 223 (2013) 40–47. doi:10.1016/j.cej.2013.02.054.

[25] T. Selkälä, J.A. Sirviö, G.S. Lorite, H. Liimatainen, Anionically stabilized cellulose nanofibrils through succinylation pretreatment in urea-lithium chloride deep eutectic solvent, ChemSusChem. 9 (2016) 3074–3083. doi:10.1002/cssc.201600903.

[26] X. Tang, M. Zuo, Z. Li, H. Liu, C. Xiong, X. Zeng, Y. Sun, L. Hu, S. Liu, T. Lei, L. Lin, Green processing of lignocellulosic biomass and its derivatives in deep eutectic solvents, ChemSusChem. 10 (2017) 2696–2706. doi:10.1002/cssc.201700457.

[27] N. Mahfoudhi, S. Boufi, Nanocellulose as a novel nanostructured adsorbent for environmental remediation: A review, Cellulose. 24 (2017) 1171–1197. doi:10.1007/s10570-017-1194-0.

[28] S. Olivera, H.B. Muralidhara, K. Venkatesh, V.K. Guna, K. Gopalakrishna, Y. Kumar K., Potential applications of cellulose and chitosan nanoparticles/composites in wastewater treatment: A review, Carbohydr. Polym. 153 (2016) 600–618. doi:10.1016/j.carbpol.2016.08.017.

[29] A.W. Carpenter, C.-F. de Lannoy, M.R. Wiesner, Cellulose Nanomaterials in Water Treatment Technologies, Environ. Sci. Technol. 49 (2015) 5277–5287. doi:10.1021/es506351r.

[30] W. Maatar, S. Alila, S. Boufi, Cellulose based organogel as an adsorbent for dissolved organic compounds, Ind. Crops Prod. 49 (2013) 33–42. doi:10.1016/j.indcrop.2013.04.022.

[31] S. Makzoom, M. Jonoobi, F. Rafieyan, H. Pourzamani, Evaluating the efficiency of cellulose nanofibers in DEHP removal from water, Desalination Water Treat. 77 (2017) 229–236. doi:10.5004/dwt.2017.20777.

[32] P.G. Moradeeya, M.A. Kumar, R.B. Thorat, M. Rathod, Y. Khambhaty, S. Basha, Nanocellulose for biosorption of chlorpyrifos from water: Chemometric optimization,

kinetics and equilibrium, Cellulose. 24 (2017) 1319–1332. doi:10.1007/s10570-017-1197-x.

[33] M. Rathod, S. Haldar, S. Basha, Nanocrystalline cellulose for removal of tetracycline hydrochloride from water via biosorption: Equilibrium, kinetic and thermodynamic studies, Ecol. Eng. 84 (2015) 240–249. doi:10.1016/j.ecoleng.2015.09.031.

[34] S. Katz, R.P. Beatson, A.M. Scallan, The determination of strong and weak acidic groups in sulphate pulps, Sven. Papperstidning. 87 (1984) R48–R53.

[35] A. Rattaz, S.P. Mishra, B. Chabot, C. Daneault, Cellulose nanofibres by sonocatalysed-TEMPO-oxidation, Cellulose. 18 (2011) 585–593. doi:10.1007/s10570-011-9529-8.

[36] T. Suopajärvi, H. Liimatainen, O. Hormi, J. Niinimäki, Coagulation–flocculation treatment of municipal wastewater based on anionized nanocelluloses, Chem. Eng. J. 231 (2013) 59–67. doi:10.1016/j.cej.2013.07.010.

[37] R. Imboden, G. Imanidis, Effect of the amphoteric properties of salbutamol on its release rate through a polypropylene control membrane, Eur. J. Pharm. Biopharm. 47 (1999) 161–167. doi:10.1016/S0939-6411(98)00053-8.

[38] S.H. Venäläinen, H. Hartikainen, Retention of metal and sulphate ions from acidic mining water by anionic nanofibrillated cellulose, Sci. Total Environ. 599–600 (2017) 1608–1613. doi:10.1016/j.scitotenv.2017.05.009.

[39] J.A. Sirviö, T. Hasa, T. Leiviskä, H. Liimatainen, O. Hormi, Bisphosphonate nanocellulose in the removal of vanadium(V) from water, Cellulose. 23 (2016) 689–697. doi:10.1007/s10570-015-0819-4.

[40] T. Suopajärvi, H. Liimatainen, M. Karjalainen, H. Upola, J. Niinimäki, Lead adsorption with sulfonated wheat pulp nanocelluloses, J. Water Process Eng. 5 (2015) 136–142. doi:10.1016/j.jwpe.2014.06.003.

[41] M. Alimohammady, M. Jahangiri, F. Kiani, H. Tahermansouri, Molecular modeling, pKa and thermodynamic values of asthma drugs, Med. Chem. Res. 27 (2018) 95–114. doi:10.1007/s00044-017-2038-z.

[42] F. Gellerstedt, P. Gatenholm, Surface properties of lignocellulosic fibers bearing carboxylic groups, Cellulose. 6 (1999) 103–121.

[43] D.J. de Ridder, A.R.D. Verliefde, S.G.J. Heijman, J.Q.J.C. Verberk, L.C. Rietveld, L.T.J. van der Aa, G.L. Amy, J.C. van Dijk, Influence of natural organic matter on equilibrium adsorption of neutral and charged pharmaceuticals onto activated carbon, Water Sci. Technol. 63 (2011) 416. doi:10.2166/wst.2011.237.

[44] G.Z. Kyzas, A. Koltsakidou, S.G. Nanaki, D.N. Bikiaris, D.A. Lambropoulou, Removal of beta-blockers from aqueous media by adsorption onto graphene oxide, Sci. Total Environ. 537 (2015) 411–420. doi:10.1016/j.scitotenv.2015.07.144.