Review

Urea removal strategies for dialysate regeneration in a wearable artificial kidney

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ABSTRACT

The availability of a wearable artificial kidney (WAK) that provides dialysis outside the hospital would be an important advancement for dialysis patients. The concept of a WAK is based on regeneration of a small volume of dialysate in a closed-loop. Removal of urea, the primary waste product of nitrogen metabolism, is the major challenge for the realization of a WAK since it is a molecule with low reactivity that is difficult to adsorb while it is the waste solute with the highest daily molar production. Currently, no efficient urea removal technology is available that allows for miniaturization of the WAK to a size and weight that is acceptable for patients to carry. Several urea removal strategies have been explored, including enzymatic hydrolysis by urease, electro-oxidation and sorbent systems. However, thus far, these methods have toxic side effects, limited removal capacity or slow removal kinetics. This review discusses different urea removal strategies for application in a wearable dialysis device, from both a chemical and a medical perspective.

1. Introduction

End stage kidney disease (ESKD) is a severe life-threatening disease that affects approximately 3 million patients worldwide [1]. Kidney transplantation is the optimal treatment, but the median wait time for a first kidney transplant is 3.6 years in the US [2], graft failure rate is high [3] and not every patient is eligible for kidney transplantation. Thus, the majority of patients with ESKD relies on hemodialysis (HD) or peritoneal dialysis (PD) to replace kidney function for a certain period of time (Fig. 1). The quality of life of dialysis patients is poor due to a high morbidity and high treatment burden [4]. The vast majority of patients (88% [5]) is treated with intermittent in-center HD (3 × 4 h per week), resulting in inadequate removal of waste solutes and excess water, which are normally excreted continuously by the healthy kidneys via the urine. Accumulation of waste solutes causes uremic symptoms, such as nausea and pruritus (itchy skin) that markedly decrease patients' well-being. Importantly, retained waste solutes exert toxic effects to multiple organs, particularly those of the cardiovascular

system [6,7]. Fluid overload is associated with hypertension, heart failure and mortality [8]. To limit accumulation of water and waste solutes, dialysis patients have to adhere to strict fluid and dietary restrictions, which further compromise their quality of life [9,10]. In addition, the time spent travelling to the dialysis center and dialysis procedure, significantly limits patients' freedom and autonomy. PD provides more continuous renal replacement therapy outside the hospital. However, the level of blood purification (or clearance, i.e. the volume of body water that is cleared of a solute per time unit) is relatively low for patients that undergo this treatment [11]. Moreover, most patients can be treated with PD for only a limited period of time due to functional decline of the peritoneal membrane, primarily caused by exposure to toxic high glucose concentrations in PD solutions, and recurrent infection of the peritoneal membrane. As a consequence, patients that are treated with PD have to switch to HD after a median of 3.7 years [12].

A wearable artificial kidney (WAK) that could provide more frequent (up to permanent) high toxin clearance outside the hospital
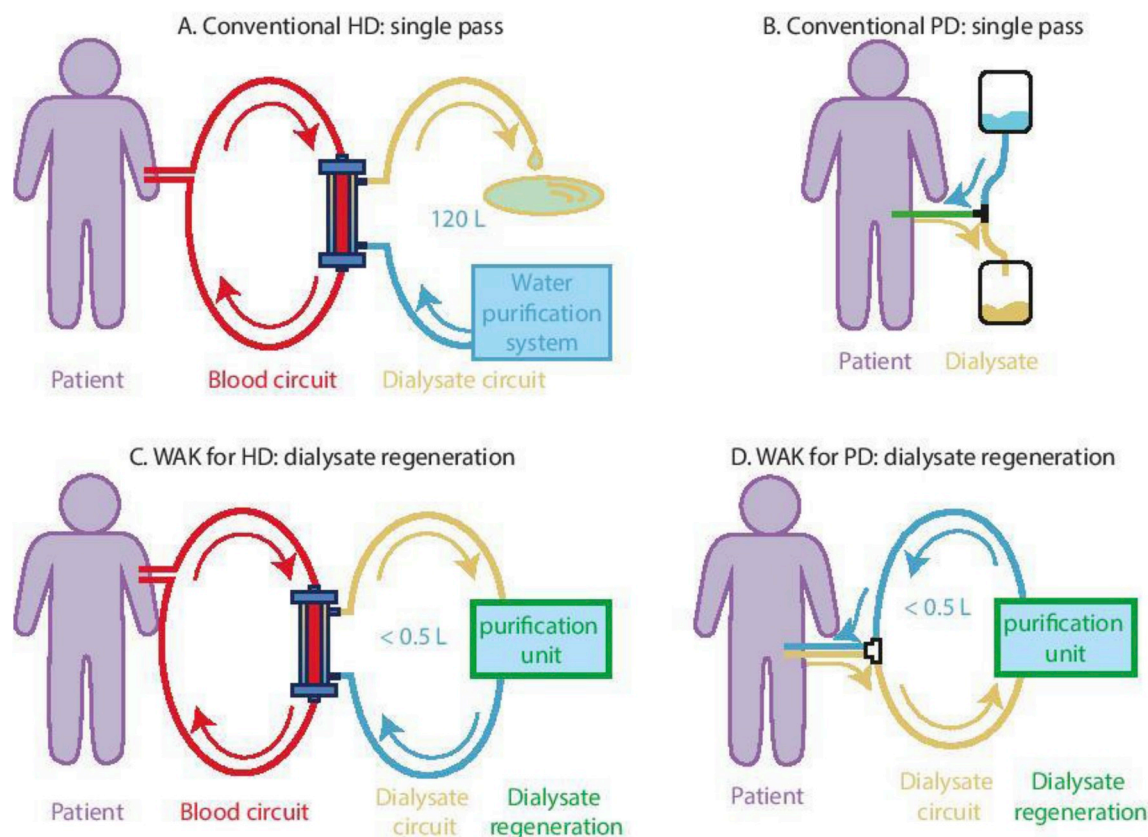
Fig. 1. A) Schematic representation of conventional single-pass hemodialysis (HD). During HD, patient's blood is circulated through a dialyzer, in which solutes pass across a semi-permeable membrane by diffusion and convection into an aqueous solution called dialysate. Dialysate in turn flows in counter-current direction to maximize the diffusive mass transport across the membrane, and is discarded into the sewage system after a single pass through the dialyzer. B) Schematic representation of conventional peritoneal dialysis (PD). During PD, hypertonic dialysate is instilled into the peritoneal cavity *via* a catheter to allow for diffusive and convective removal of waste solutes and osmotic removal of excess water across the peritoneal membrane. After a certain period of time, the dialysate (containing waste solutes and excess water) is drained and discarded. C and D) Schematic representation of a wearable artificial kidney (WAK) with dialysate regeneration. Spent dialysate is continuously regenerated by a purification unit and reused.

would be a considerable improvement for both HD and PD patients. Such a small dialysis device, preferably less than 2.0 kg when worn on the body [13] or less than 11 kg when used as a table device (*i.e.* the advised maximum weight to lift for PD patients [14]), will substantially increase patients' mobility, freedom and ability to engage in social and economic life. Importantly, more frequent or continuous treatment with a WAK will possibly reduce waste solute concentrations and fluctuations of patients' internal environment and fluid status and may therefore improve clinical outcomes, in terms of quality of life, survival, hospitalization rates, left ventricular mass, blood pressure, bone mineral metabolism and medication burden, as observed with more frequent or prolonged HD [15–19].

The key for the development of a WAK is efficient regeneration of dialysate from patients (i.e. spent dialysate) in a closed-loop system (Figs. 1 and 2). Regeneration of spent dialysate will allow for the use of a small volume of dialysate (ideally less than 0.5 L), whereas conventional single-pass HD uses a large volume of dialysate (approximately 120 L per 4-h HD session) typically produced by a stationary water treatment system. Traditional PD requires a considerable volume of bagged dialysis fluids (8–12 L per day) to be stored at the patients' home. Dialysate regeneration entails removal of uremic solutes from spent dialysate and maintenance of stable dialysate pH and electrolyte concentrations. The solutes that need to be removed to regenerate the dialysate are uremic waste solutes that are normally excreted by the healthy kidneys and are transported to the dialysate during dialysis. This includes ions, such as phosphate and potassium which accumulation leads to vascular calcification and (lethal) arrhythmia,

respectively, and organic solutes, such as small nitrogenous waste products (e.g. urea, creatinine) and low molecular weight proteins (e.g. β2-microglobulin, a protein associated with dialysis related amyloidosis). Of note, highly protein bound uremic toxins are hardly removed by dialysis in general since these solutes are primarily bound to albumin (66 kDa) that does not pass the semipermeable membrane separating the dialysate and the blood. Phosphate and potassium ions are removed from spent dialysate by ion-exchangers and most organic waste solutes can efficiently be removed by activated carbon (AC) [20,21]. Importantly, the affinity of AC for urea is relatively low (0.1–0.2 mmol/g, see paragraph 5) [22,23] while daily molar production of urea is higher than that of other waste solutes (240–470 mmol per day) [24,25]. As a consequence, the greatest challenge for efficient dialysate regeneration is urea removal [26]. The aim of this review is to discuss strategies to remove urea from dialysate that can be applied in a WAK (*i.e.* enzymatic hydrolysis, electrochemical oxidation (EO), chemisorption and physisorption) and the advantages, disadvantages and possible improvements of these methods both from a chemical and clinical perspective.

2. Urea

In the human body, proteins and other nitrogen-containing nutrients are metabolized into ammonium, which is converted in the liver into urea *via* the urea cycle [27]. Urea is transported to the kidneys through the bloodstream, where it is excreted into the urine [28]. Urea is the main circulating non-protein nitrogen compound and accounts
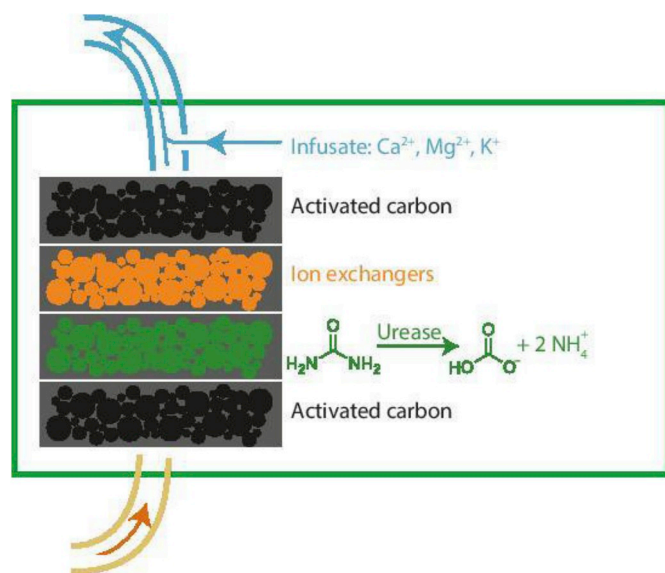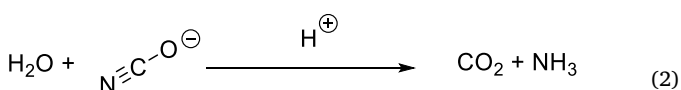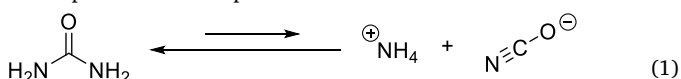
Fig. 2. Schematic overview of a urease-based sorbent system purification unit that contains activated carbon for adsorption of non-urea organic compounds, immobilized urease that catalyzes the hydrolysis of urea into ammonium and (bi)carbonate, a cation-exchanger that binds cations (including ammonium, calcium, magnesium, and potassium) in exchange for sodium or hydrogen cations, and an anion-exchanger that binds phosphate in exchange for hydroxide, bicarbonate and/or acetate anions. Finally, calcium, magnesium and potassium ions (in the form of their chloride salts) are infused to reconstitute the dialysate.
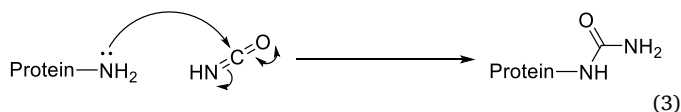
for approximately 90% of renal nitrogen excretion [24]. It is the waste solute with the highest daily molar production of 240–470 mmol, depending on protein intake [24,25]. Since elevated plasma urea concentrations (20–30 mM), representative for ESKD, are associated with toxicity [29], effective urea removal is crucial for successful dialysate regeneration.

In general, urea is a very unreactive metabolite: urea is uncharged at physiological pH and is neither very nucleophilic nor electrophilic. To enable urea to act as a nucleophile, a very strong electrophile is needed (as discussed in paragraph 5). The spontaneous hydrolysis of urea (thus acting as an electrophile) in aqueous solution is very slow unless catalyzed by urease (as discussed in paragraph 3). In aqueous solution urea is in equilibrium with traces of the fragmentation products ammonium and cyanate (0.1–0.8%) (reaction (1)) [31]. In principle, cyanate can further react with H_2O under acidic conditions to form CO_2 and NH_3 (reaction (2)). However, under physiological conditions, the reaction of cyanate with H_2O is very slow and ammonium and cyanate fragmentation products remain present to a minor extent.

$$\underset{H_2N}{\overset{O}{\parallel}}{}_{NH_2} \rightleftharpoons \overset{\oplus}{N}H_4 + N\!\equiv\!C\!-\!O^{\ominus} \tag{1}$$

$$H_2O + N\!\equiv\!C\!-\!O^{\ominus} \xrightarrow{H^{\oplus}} CO_2 + NH_3 \tag{2}$$

Urea is a chaotropic agent that can disrupt the globular structure of proteins by breaking hydrogen bonds, thereby altering protein and enzyme function [29,32]. Although mildly elevated urea concentrations in the range of 10–20 mM are well tolerated, uremic concentrations above 20 mM have been associated with toxicity, including insulin resistance, disruption of the gastrointestinal barrier which may result in leakage of pro-inflammatory mediators from the gut into the bloodstream, production of radical oxygen species, induction of apoptosis and death of smooth muscle cells, and endothelial changes promoting atherosclerosis [29]. These effects are either caused by urea directly, by cyanate or ammonium (reactions (1) and (2)), or as a result of the reaction of isocyanic acid (conjugated acid of cyanate) with arginine or

lysine residues in proteins (carbamylation) [33], as shown in reaction (3).

$$\text{Protein}\!-\!\overset{..}{N}H_2 \quad HN\!=\!C\!=\!O \longrightarrow \text{Protein}\!-\!NH\overset{O}{\overset{\parallel}{\,}}NH_2 \tag{3}$$
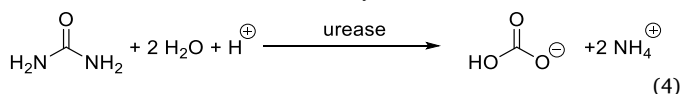
Carbamylated proteins cause a variety of biochemical alterations, including transition of mesangial cells into a profibrogenic cell type, altered leukocyte response (caused by carbamylated collagen), vascular damage (caused by carbamylated low-density lipoprotein) and abnormal erythropoietin response (caused by carbamylated erythropoietin). Therefore, high urea concentrations should be avoided [29]. To remove the daily urea production of 240–470 mmol [24,25], while keeping the urea concentration below 20 mM with a daily 8-h dialysis regime, urea clearance during dialysis should be at least 25–49 mL/min, respectively, resulting in a 24-h time-averaged clearance of 8–16 mL/min.

3. Enzymatic hydrolysis of urea

3.1. Ureases

Krajewska published extensive reviews on ureases, their binding pockets, catalytic properties and their inhibitors [34,35]. Most ureases found in plants and fungi are present as a trimer or hexamer of subunits with a molecular weight of ca. 90 kDa per subunit and have a hydrodynamic diameter of ca. 14 nm [34,36]. Ureases use a zinc-ion to coordinate the carbonyl group of urea, making the carbonyl group more electrophilic. While urea is very stable in physiological aqueous solutions towards chemical hydrolysis (pH 7.4 and 37 °C) [34]), urease-catalyzed hydrolysis of urea into ammonium and bicarbonate (reaction (4)) is very efficient. Urease derived from jack beans (*canavalia ensiformis*) is one of the most active ureases. This enzyme follows Michaelis-Menten kinetics, has a relatively low K_M of 2.9–3.6 mM, *i.e.* the substrate concentration at which urease activity is 50% of the maximum activity, and is most active at a pH of 7.0–7.5 [34]. The turnover rate of urease is up to 5.9×10^3 s^{-1} [37–39], while the rate of uncatalyzed urea hydrolysis is too slow to determine experimentally and independent of the pH in the range of 4–10 [40,41]. Since the dialysate urea concentration is ~10–30 mM (thus, far above the K_M) and pH of the dialysate is around 7.4, the activity of urease is close to V_{max} in dialysate. Based on these values, in theory, only ~3–5 mg of active urease is sufficient for complete removal of urea from dialysate during a 4-h dialysis session at dialysate flow rates up to 300 mL/min and urea concentrations ranging from 2 to 40 mM. However, it was found empirically that ~30–50 g of immobilized urease (including matrix) is needed to accomplish this (unpublished data). Therefore, enzymatic urea hydrolysis would be a very attractive approach to remove urea from dialysate [42,43]. However, the formed ammonium is much more toxic than urea itself. Therefore, a urea removal strategy based on urease should be complemented with a strategy to remove ammonium, as discussed in the "the REDY sorbent system" section.

$$\underset{H_2N}{\overset{O}{\parallel}}{}_{NH_2} + 2\,H_2O + H^{\oplus} \xrightarrow{\text{urease}} \underset{HO}{\overset{O}{\parallel}}{}_{O^{\ominus}} + 2\,\overset{\oplus}{N}H_4 \tag{4}$$

3.2. Urease immobilization

Immobilization of urease onto a solid support is essential for the development of a urease-based WAK. Urease immobilization has been reviewed by Krajewska [35] and can be achieved by chemical (covalent bonding) or physical immobilization (non-covalent bonding). In general, immobilization reduces V_{max} and increases K_M. A higher urease activity level is usually maintained by physical immobilization as

compared to chemical linkage to a carrier. Urease has been chemically immobilized on porous chitosan/glutaraldehyde beads [44], poly(*N*-isopropylacrylamide-*co*-*N*-acryloxysuccinimide-*co*-2-hydroxyethyl methacrylate) hydrogels [45], poly-acrylonitrile hollow fibers [46,47], beads based on poly(acrylamide-*co*-acrylic acid [48], poly-vinylalcohol [49], gelatin [50], microporous epoxy-functionalized methacrylamide copolymer (Eupergit®) [51] and cellulose [52]. In addition, it has been physically immobilized on AC, Al_2O_3 and zirconium phosphate [53,54]. The different immobilization methods are associated with varying strengths of the bond between support material and enzyme. Physical immobilization is weakest, and is considered easily reversible. Chemical immobilization is generally better, although certain covalent bonds used for chemical immobilization, e.g. the imine-linkages formed by the reaction of glutaraldehyde with amino-groups of urease, are hydrolyzable (i.e. reversible) under the conditions found in dialysate. The preferred option for application in a wearable artificial kidney is therefore immobilization through non-hydrolyzable chemical linkers, for example through amine or ether bonds formed between urease and epoxy-substituted support materials.

Depending on the reaction conditions, epoxy-substituted support materials can form covalent bonds with carboxylic acid-, thiol-, amino- or phenolic groups of the enzyme. Bortone et al. reported that single-point immobilization of urease on Eupergit® by epoxy coupling slightly reduced the enzyme's binding constant (Michaelis constant) K_M for urea from 3 mM to 5 mM [34,51] while the constant for the conversion of urea to ammonium (k_{cat}) remained approximately unchanged. The activity of the enzyme was reduced by factor 2 upon immobilization as a result of limited diffusion of urea (and therefore a local urea concentration lower than K_M in the sorbent).

3.3. The REDY sorbent system

Until now, the REcirculation DialYsis (REDY) sorbent system [55], which contains urease (derived from jack beans and physically immobilized on aluminum oxide (Al_2O_3)) for enzymatic conversion of urea, is the only dialysate regeneration system that has been marketed. From 1973 to 1994, more than six million treatments were successfully performed with this transportable (approximately 20 kg) dialysis system, demonstrating the clinical feasibility of HD with dialysate regeneration [56]. However, manufacturing of the REDY sorbent system was discontinued in 1994. The relatively high costs of the disposable sorbent cartridges, inferior treatment adequacy compared to single-pass dialysis as a result of limited dialysate flow rates (max. 250 mL/min) and concerns about aluminum-induced osteomalacia (bone softening) and dementia may have contributed to this [57–61].

Dialysate regeneration with the REDY sorbent system has been described in detail by Agar [20], Ash [21] and others [62–64]. In brief, dialysate passes several sorbent layers, starting with AC which adsorbs non-urea organic compounds. Next, urea is hydrolyzed by immobilized urease into ammonium and (bi)carbonate. Subsequently, ammonium is exchanged for sodium or hydrogen cations by a zirconium phosphate ion-exchanger [65]. Finally, zirconium oxide and zirconium carbonate adsorb phosphate in exchange for hydroxide, bicarbonate and acetate. Even though urease (hydrodynamic diameter ca. 14 nm [34,36]) cannot pass the dialysis membrane (cut off 5–8 nm [66]), it is important that urease is immobilized upstream of the zirconium phosphate layer to prevent ammonium release into the patient. A schematic overview of the REDY sorbent system is shown in the review by Roberts [42].

The REDY system, however, has several drawbacks. First, following reaction (1), for every equivalent of urea, two equivalents of ammonium are formed. Thus, the daily urea production of 240–470 mmol [24,25,67] is converted into 480–940 mmol of ammonium. Moreover, ammonium is more toxic than urea [68] and a relatively large amount of zirconium phosphate (~0.5–1 kg) is required to (almost) completely bind this amount of ammonium. Second, zirconium phosphate does not only bind ammonium, but also calcium, magnesium and (too much)

potassium ions, resulting in the necessity to re-infuse these adsorbed cations from a separate reservoir [69]. Although this allows for a personalized dialysate prescription by adjustment of the calcium, magnesium and potassium ion concentrations to the patients' need, the re-infusion reservoir further increases the size and weight of the device. Third, the adsorbed cations are exchanged for hydrogen and sodium cations. The released protons may (partially) react with bicarbonate generated during urea hydrolysis to form water and carbon dioxide, which can be effectively removed from the dialysate circuit *via* a degasser [70]. Bicarbonate release into the spent dialysate is in fact favorable as it may correct for metabolic acidosis, a common complication of kidney failure due to impaired excretion of non-volatile acid. However, sodium release is a major concern as higher dialysate sodium concentrations are associated with weight gain between dialysis sessions and related complications such as hypertension [71]. To prevent a rise in dialysate sodium concentration, a sodium-free dialysate reservoir could be used to dilute the released sodium ions, although this would be at the expense of miniaturization.

In addition to the miniaturization issues, long-term treatment with the REDY system has been associated with a severe form of fracturing osteomalacia and encephalopathy (brain injury) due to leaching of aluminum ions from AC that was often contaminated with this metal [58,59,61,72,73]. In 1982, cartridges became available with reduced aluminum content that did not show aluminum release above the maximum allowable level of 0.37 μM in water for dialysate preparation according to the Association for the Advancement of Medical Instrumentation (AAMI) [74,75]. Still, urease physically immobilized onto Al_2O_3 is considered a potential hazard for chronic dialysis patients. These drawbacks and non-cost competitiveness with single-pass HD, resulted in the disappearance of the REDY system from clinical practice in 1994 [42].

3.4. "Second generation" urease-based wearable artificial kidney devices

Several research groups are currently working on REDY-like sorbent system for the development of miniature dialysis systems for both HD and PD using disposable cartridges [76]. These second-generation urease-based systems are characterized by a more stable sodium and acid-base profile compared with the original REDY sorbent system. Best known is the WAK as developed by Gura et al., which has been evaluated during two pilot clinical trials [69,77]. In the most recent trial in 2016, seven HD patients were treated with the WAK up to 24 h while being mobile [69]. The device weighed approximately 5 kg, including dialysate and sorbents (65 g physically immobilized urease on Al_2O_3, 600 g zirconium phosphate, 51 g hydrous zirconium oxide and 153 g AC). Mean plasma clearances of urea, creatinine, phosphate and β2-microglobulin per 24-h treatment compared favorably to time-averaged plasma clearances of intermittent HD [11,78]. Importantly, no serious adverse events were observed. However, several urease related technical problems were reported. In one patient after 11 h of treatment, dialysate ammonium concentration exceeded 2.9 mM, which was set as the maximum allowable concentration, indicating zirconium phosphate saturation. Plasma sodium concentration remained stable during the first 16 h of treatment (~130 mM) and tended to increase to 135 ± 4 mM (p = 0.13) after 24 h of treatment (sodium balance was not reported). Other encountered problems were excessive carbon dioxide bubbles in the dialysate circuit exceeding degassing capacity, formation of blood clots in the blood circuit and technical issues such as tubing kinking and early battery failure, which prompted early termination of the trial [11,78].

Most other miniature dialysis systems that are currently under development make use of a modified REDY-type sorbent system for dialysate regeneration [76]. AWAK Pte Ltd (Singapore and Burbank, CA) recently evaluated an automated wearable artificial kidney (AWAK PD™, < 2 kg [79]) for PD during a First-In-Human clinical trial in 14 PD patients [80]. AWAK treatment for > 10.5 h per day up to three days

resulted in a significant decrease in urea, creatinine and phosphate plasma concentrations from 20.8 to 14.9 mM (p = 0.001), 976 to 668 μM (p = 0.001) and 1.7 to 1.5 mM (p = 0.03), respectively. A weekly peritoneal K_t/V_{urea} (the volume cleared of urea over the total urea distribution volume) of >1.7 was achieved, which is the minimum K_t/V_{urea} in anuric patients recommended by the International Society of Peritoneal Dialysis guidelines [81]. Although no serious adverse events occurred, 73% of subjects experienced temporary abdominal discomfort, which resolved spontaneously after dialysate drainage or bowel movement. Importantly, plasma sodium, potassium and bicarbonate concentrations were stable, although systemic ammonium concentrations were not reported. The company Diality (formerly named Easydial) evaluated a portable (~10 kg) HD device (Dharma) and reported a mean urea reduction ratio (URR) of 78% at a plasma urea concentration of 40 mM, which is higher than the recommended minimum URR of 65% [82–85]. However, mean plasma sodium concentrations increased by 7.3 mM which is unacceptable for patients [86]. A schematic overview of a urease-based sorbent purification system is shown in Fig. 2.

4. Electrochemical decomposition of urea

In 1966, Tuwiner published a report on a water reclamation system for manned space vehicles that used electrochemical treatment to remove urea from urine [87]. This report initiated research on electro-oxidation (EO) of urea for dialysate regeneration (see Table 1 for an overview of studies). A schematic representation of an EO-based purification unit is shown in Fig. 3, in which AC is placed upstream of the EO-unit to remove most organic waste solutes. EO is in principle an attractive technique for a WAK because it converts urea into gaseous products (nitrogen, hydrogen and carbon dioxide) that can easily be removed from dialysate by a bubble trap, and, importantly, EO-modules are small in size, lightweight, have a long life time and are relatively inexpensive and potentially reusable. Evaluation of an EO-based WAK (6 A/h) in uremic goats showed that 24-h treatment would suffice to remove the daily urea production [88], which requires ~100 g of battery that delivers 25 W per hour (or, for example, 4 batteries of 600 g per day). However, the challenge for EO is control of the exact reactions and formed products, because besides the mentioned gasses also other, mainly toxic, compounds are generated, such as active chlorine species and chloramines that need to be removed by placing AC downstream of the EO-unit (Fig. 3).

4.1. Reactions and products

Direct EO of urea converts urea into nitrogen gas (N_2), carbon dioxide gas (CO_2) and hydrogen gas (H_2) (reaction (5)). This reaction is the net result of urea oxidation at the anode and simultaneous reduction

Table 1
Publications reporting electro-oxidation of urea.

Anode material	[Urea] (mM)	Applied current density (mA cm^{-2}) or potential (V)	Urea removal per unit area (mmol/h/m^2)	In vitro (S,D, sD, U, aU[a]), or *in vivo* (V)	Reference
Pt	8.7	0.5 mA cm^{-2}	2.4–5.3	S	[99]
Pt	8.3	6–18 V	4.2·10^3–7.3·10^3	D	[107]
Pt	10	a) 0.11 mA cm^{-2}	a) 7.4	S	[98]
		b) 0.22 mA cm^{-2};	b) 4.6		
		c) 0.8 V	c) 8.3		
		d) 1.0 V	d) 9.1		
		e) none	e) 2.9		
Pt	3.3	Not specified	1.1·10^2–1.9·10^2	D	[100]
Pt	33	7–20 mA cm^{-2}	5.1·10^3	D	[97]
C foil	42	25.2–39.1 mA cm^{-2}/8.5–11.5 V	1.4·10^3–1.7·10^3	–	[108]
Pt	a) 9–33;	0.88 mA cm^{-2}, ≤1.2 V; 0.64 mA cm^{-2}, ≥-1.0 V	a) 17–37	a) S	[96]
	b) 43		b) 1.4–1.5	b) sD	
Ru–Ti–Sn–O (RTTO)	0–500	4–61 mA cm^{-2}	7.0·10^2	S	[90]
Pt	12.9	10; 20; 30; 39; 49; 59 mA cm^{-2}	11–79	D	[95]
Pt	29	5 mA cm^{-2}	1.9·10^2–5.1·10^2	U	[109]
a) PtIr	a) 71.4	40 mA cm^{-2}	a) 6.0·10^2	a) aU	[91]
b) Fe and PtIr	b) NaN		b) 16–5.3·10^2	b) U	
a) (Pt–Ir)$_{70:30}$	0–167	20–100 mA cm^{-2}	a) 1.4·10^3–3.4·10^3	S	[110]
b) (Ta$_2$O$_2$–IrO$_2$)$_{70:30}$			b) 78–3.1·10^3		
a) Pt	17–167	2–10 mA cm^{-2}	a) 1.4·10^3–4.8·10^3	S	[111]
b)(RuO$_2$–TiO$_2$)$_{40:60}$			b) 1.1·10^3–3.3·10^3		
Ti/IrO$_2$	266	15 ± 0.3 mA cm^{-2}	4.4·10^2–7.1·10^2	U	[112]
BiO$_x$/TiO$_2$	41.6	a) 2.0 V	a) 0.53	S	[113]
		b) 2.8 V	b) 4.7–8.9		
a) Pt	a) 20	a) 10 mA cm^{-2}	a) 7.3·10^2	a) S	[89]
b) RuO$_2$	b) 20	b) 10 mA cm^{-2}	b) 4.5·10^2	b) S	
c) Graphite	c) 5–30	c) 6.8–17 mA cm^{-2}	c) 1.7·10^2–4.8·10^2	c) S	
d) Graphite	d) ~20	d) 10 mA cm^{-2}	d) 3.2·10^2	d) sD	
a) Pt	0.03	5–20 mA cm^{-2}	a) 32–4.2·10^2	S	[105]
b) Ti–RuO$_2$			b) –		
c) SnO$_2$–Sb$_2$O$_5$			c) 61–1.0·10^3		
c) BDD			d) 1.7·10^2–1.5·10^3		
a) BDD	200	40 mA cm^{-2}	a) 700	aU	[114]
b) IrO$_2$			b) –		
a) Graphite	30	5 mA cm^{-2}	a) 2.5·10^2	S	[115]
b) BDD			b) 2.5·10^2		
c) MoDD			c) 2.5·10^2		
d) Si/C			d) 2.5·10^2		
e) Si/C/Fe			e) –		
f) Si/C/Mo			f) 3.2·10^2		
g) Pt			g) 1.2·10^2		
Graphite	7–14	10 mA cm^{-2}	96–1.8·10^2	V	[88]

[a] S, salt solution; D, unused dialysate with added urea; sD, spent dialysate; U, urine; aU, artificial urine.

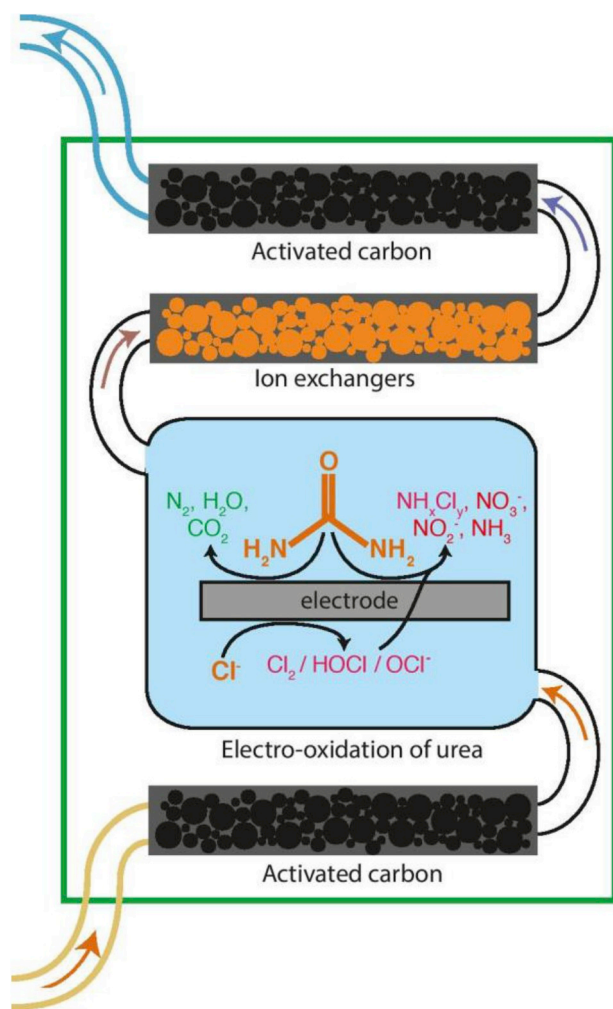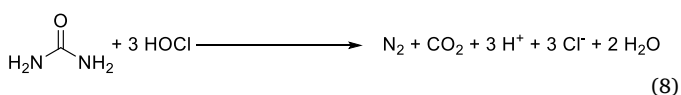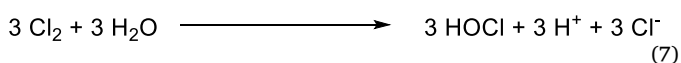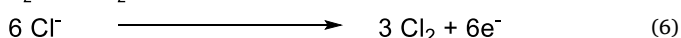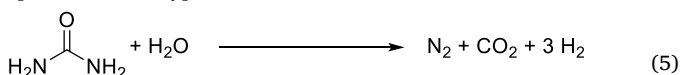**Fig. 3.** Schematic representation of an electro-oxidation based WAK. Activated carbon is placed upstream of the electrodes to remove competing solutes for oxidation at the anode, which may reduce the efficiency of urea oxidation. In addition, activated carbon is placed downstream of the electrodes to remove oxidative by-products. Products of complete urea oxidation are presented in green, unwanted toxic by-products of urea oxidation are presented in red. Cation and anion ion-exchangers bind potassium and phosphate ions, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of water at the cathode. When chloride ions (Cl^-) are present in the solution, as is the case in dialysate, the oxidation of urea can occur *via* a second indirect route, mediated by anodically generated active chlorine species such as hypochlorite (OCl^-) [89,90].

$$H_2N-CO-NH_2 + H_2O \longrightarrow N_2 + CO_2 + 3\,H_2 \tag{5}$$

$$6\,Cl^- \longrightarrow 3\,Cl_2 + 6e^- \tag{6}$$

$$3\,Cl_2 + 3\,H_2O \longrightarrow 3\,HOCl + 3\,H^+ + 3\,Cl^- \tag{7}$$

$$H_2N-CO-NH_2 + 3\,HOCl \longrightarrow N_2 + CO_2 + 3\,H^+ + 3\,Cl^- + 2\,H_2O \tag{8}$$

Ideally, the indirect reactions (6)–(8) result in the same products as the direct route, i.e. nitrogen, carbon dioxide and hydrogen gas. However, in most cases, at least trace amounts of toxic side products such as nitrate (NO_3^-), nitrite (NO_2^-), ammonia (NH_3), chloramines (NH_xCl_y) and active chlorine species are formed. Nitrate may cause

gastric cancer in adults and methemoglobinemia in infants [91,92]. Ammonia is toxic for many organs, particularly the brain [68]. Chloramines, which are derivatives of ammonia by substitution of hydrogen with chlorine atoms, may cause oxidative damage to red blood cells and shorten their survival resulting in anemia [93]. Furthermore, active chlorine species have strong oxidizing properties and can react with proteins [94] and other components of the dialysate to form toxic chlorine products. Most of these products can be removed with AC, but considering their reactivity and toxicity, it is preferable to prevent their formation.

Another factor to consider is undesired oxidation of other dialysate components, which may also result in the formation of potentially hazardous products. An example is oxidation of glucose into aldehydes, which occurs more readily than oxidation of urea, as observed in a number of studies [88,95–100]. For PD, aldehydes are associated with pathological changes of the peritoneal membrane [101,102]. Consequently, to render EO suitable for dialysate regeneration, control over reactions and their products is paramount. Key parameters which can be used to control the reactions and products are the electrode material, applied potential, and applied current density. In the following paragraphs we will discuss these parameters and how they affect the formation of unwanted products. Subsequently, the efficacy of urea removal and the current efficiency will be discussed.

4.2. Electrode material

The electrode material has to meet several requirements. First, it needs to be chemically stable to ensure its continuous operation for at least several days. Hence, corrosion or degradation is highly undesirable. Second, the material should not leach toxic metals, as has been observed for platinum and ruthenium electrodes [89,98,103]. Third, the ideal electrode material should be selective, favoring the desired reaction and hardly catalyze undesired reactions. The electrode material determines to some extent which reactions can take place. Often, reagents need to bind to the electrode surface in a specific configuration before electron transfer between the reagent and electrode can take place. Furthermore, the potential at which reactions occur is electrode material dependent which means that the order in which reagents react can vary with the electrode material. For example, platinum is a known catalyst of many reactions, among which chloride and water oxidation which occur at lower potentials on platinum electrodes than on non-catalytic materials. Water oxidation in the WAK is undesired, because this will greatly reduce the current efficiency (see below) and results in formation of oxygen bubbles that can block the anode. Conversely, boron-doped diamond electrodes do not catalyze water oxidation, but generate hydroxyl radicals with high efficiency [104]. Hydroxyl radicals in turn can act as mediators in the indirect oxidation of urea, just like active chlorine species [105]. Wester et al. compared platinum, ruthenium and graphite electrodes and found graphite to be the most favorable because of its acceptable urea removal rate with limited chlorine formation [89]. Researchers from Lockheed Inc. investigated over 50 anode materials for their corrosion resistance in electro-chemical treatment of urine. They found that 10% rhodium-containing platinum was the optimal electrode material based on corrosion resistance and current efficiency [103]. In addition, various cathode materials were studied for urine pretreatment and platinum was selected as the best, because of its low overpotential for hydrogen evolution [103]. This means that closing the current loop by reactions at the counter electrode will readily occur through hydrogen evolution from water reduction, making it possible for this electrode to sustain large current densities without undesired side reactions taking place. Other materials that have been investigated for their applicability as anode for EO of urea, for either dialysate regeneration or waste water treatment, are listed in Table 1. Publications on waste water regeneration under physiological conditions are included, since urea removal from urine is comparable to dialysate regeneration. Recently,
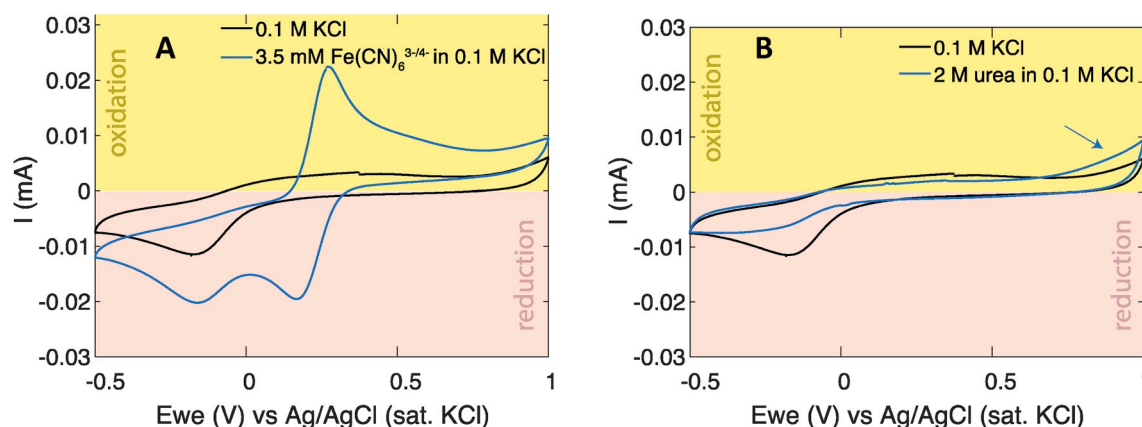
Fig. 4. Cyclic voltammograms of A) 0.1 M KCl and 3.5 mM ferro/ferricyanide in 0.1 M KCl; and B) 0.1 M KCl and 2 M urea in 0.1 M KCl (unpublished data). The arrow indicates a slight increased oxidation current at potentials >0.7 V in the presence of urea, likely due to increased chloride oxidation. Ewe: potential applied (E) to the Pt working electrode (we). Scan rate was 100 mV/s.

nickel-based electrodes have received a lot of attention in waste water treatment due to their efficient urea oxidation capacity [106]. However, these electrodes only function at or above pH 9, and are therefore unsuitable for dialysate regeneration at physiological conditions (pH 7.4–8.0). Besides the electrode material, functionalization of the electrode surface with catalytic groups or incorporation of selective membranes may increase selectivity of the reaction at the electrode.

4.3. Oxidation potential of urea

Whether or not a species such as urea can be oxidized at the anode is primarily dependent on the applied potential, which has to be high enough to overcome the oxidation potential of urea. However, the exact oxidation potential is unknown, as discussed below. Cyclic voltammetry (CV) is routinely used to determine the oxidation potential of compounds. During CV a potential scan is performed and the resulting current is measured. When the oxidation potential is approached, oxidation of the tested compound occurs, which in turn results in an increase of the current. At higher potentials, all available molecules of the oxidizable species near the electrode surface are instantly depleted and oxidation becomes diffusion limited resulting in a decrease of the current. CV diagrams therefore often have distinctive shapes, with clear oxidation peaks, see Fig. 4A. Unfortunately, urea does not produce such a sharp oxidation peak in the CV diagram, but a small increase in current over a wide range of potentials is observed, see Fig. 4B for an example [89,91,99,110,111].

For platinum electrodes, changes in currents for urea were reported between 0.5 and 0.9 V *vs* Ag/AgCl[2] [96,98,110,116,117]. Since chloride was present in the urea solutions and the standard potential of chloride oxidation is in the same range (0.6–1.2 V) [118], the increased currents could be due to oxidation of chloride, resulting in indirect oxidation of urea (reactions (6)–(8)). Formation of hypochlorite was not detected below 1.2 V, but this may be due to complete consumption of hypochlorite by (indirect) urea oxidation at lower potentials. Reports of CV in the absence of chloride are rare, likely because chloride is unavoidable in reported applications of EO for urea removal such as dialysis regeneration and waste water treatment. Hernandez et al. performed CV in a sodium perchlorate solution and reported increased currents on platinum electrodes between 0.7 and 1.2 V, suggesting that the oxidation potential of urea lies within this range for platinum electrodes [105]. On the other hand, using Ti–RuO$_2$-electrodes at the

same voltages, only urea adsorption and no urea oxidation was observed [105]. On boron doped diamond (BDD) and SnO$_2$–SbO$_5$ electrodes neither direct urea oxidation, nor adsorption of urea was observed, but water oxidation occurred, suggesting indirect oxidation of urea by the formed hydroxyl radicals [105]. The observation that urea can be oxidized by active chlorine and hydroxyl radicals suggests that the oxidation potential of urea is lower than that of chloride (0.6–1.2 V) and water (1.0 V). Nevertheless, direct oxidation of urea does not readily occur on the investigated materials under physiological conditions. This may be due to blocking of the electrode surface by strongly adsorbed urea on materials such as platinum, and lack of adsorption of urea and therefore lack of interaction with the electrode surface for other materials. Taken together, due to the presence of chloride in the dialysate and no or minimal direct oxidation of urea below chloride oxidation potentials with the electrode materials tested thus far, the best strategy for electrochemical dialysate regeneration needs to be focused on indirect urea oxidation. However, if a material would be found, which enables direct oxidation of urea, this could theoretically increase the efficiency and safety of the process. Unfortunately, such a material has not been identified so far.

4.4. Current driven and potential driven mode

Electro-oxidation can be performed in a current or a potential driven mode. This means that either the current or the potential at the anode can be set, and the other follows as a result of the setting and therefore cannot be independently selected. The magnitude of the potential difference between anode and cathode determines which reactions take place and only (combinations of) reactions with an oxidation potential lower than the potential difference between the electrodes occur.

4.5. Current driven mode and current density

In most publications a current driven mode is used, probably because this is the easiest to implement. At the electrode-electrolyte interface electrons have to be transferred to molecules or ions through a redox reaction resulting in oxidation of molecules at the anode and simultaneous reduction at the cathode. First, the most reactive species, i.e. the species with the lowest oxidation potentials, will participate in this reaction. When these species are depleted, the potential difference between the electrodes increases resulting in oxidation of less reactive species. This gives little control over the exact reactions and carries a high risk of undesired side reactions such as electrolysis of water.

Since electron transfer occurs at the electrode surface, the surface area of the electrode is an important determinant of the reactions.

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[2] All potentials in this review are given relative to the Ag/AgCl reference electrode ($E^0_{Ag/AgCl, \ sat \ KCl}$ = 0.197 V *vs* standard hydrogen electrode, SHE). Where literature mentions Ag/AgCl without giving the chloride concentration, saturated KCl is assumed.

When the same current can be divided over twice the surface area, twice as many molecules of the reactive species are available for reaction. The applied current is therefore normally expressed as *current density*: the current per unit electrode area. Thus, there are two ways to decrease undesired side reactions: (1) increasing the concentration of the desired reagent, or (2) decreasing the current density. Of note, increasing the concentration at or in the vicinity of the electrode surface can also be achieved by active convection such as stirring or application of flow over the electrode surface.

In the case of indirect oxidation of urea by active chlorine species, the oxidation of chloride is desired yielding active chlorine species which in turn decompose urea, but also result in the formation of unwanted by-products such as chloramines. Controlling the ratio of urea supply *vs* current density is therefore of utmost importance. When the current density is too low, insufficient amounts of active chlorine will be formed, which leads to incomplete urea oxidation and accumulation of intermediate products such as chloramines. When the current density is too high, this results in excess formation of active chlorine, which increases the concentration of undesired active chlorine in the effluent. Thus, there is a delicate balance between incomplete oxidation, complete oxidation and over-chlorination. The challenge is to determine the point at which chlorine levels exceed the oxidant demand and free chlorine starts to build up in the dialysate, which is called break-point chlorination.

4.6. Potential driven mode and pulsed-potential techniques

In the potential driven mode, a fixed potential is applied at the anode which is in contrast with the current driven mode where there is no control over the potential difference that develops between the electrodes. The potential driven mode has been less widely used in literature, likely because it depends on a three electrode system, in which besides a cathode and anode also a reference electrode is used. In potential driven oxidation, the potential at the anode relative to the reference electrode can be used to tailor which reactions occur, since no reaction with an oxidation potential higher than the applied potential will take place. The potential at the cathode changes to accommodate the current needed to sustain the anodic potential but the potential at the cathode is otherwise not controlled. For removal of urea, the anode potential should be set at such a value that urea oxidation occurs, but not higher to prevent side reactions such as water oxidation. However, the potential at which urea oxidation occurs is relatively high (>0.7 V), which implies that not all side reactions can be avoided.

An alternative method, which may improve the selectivity of EO for urea in dialysate is the application of pulsed potentials [119,120]. For lidocaine it was found that oxidation by potential pulses (of 3.0 V *vs* Ag pseudo-reference electrode) considerably enhanced the yield of the reaction products as compared to a continuous potential (of 3.0 V *vs* Ag). Tuning of the cycle time modulated the selectivity of the oxidation reaction (more 4-hydroxylation product at cycle times of 0.2–12 s and more N-dealkylation product at cycle times <0.2 s) [119]. The increased selectivity for certain reaction paths is likely a result of a more active electrode surface, since the surface is rapidly passivated under oxidative conditions during the pulse, but recovers between the pulses at the lower potential. The same may hold for urea oxidation, where adsorption and deactivation of the platinum electrode surface is a known phenomenon [79]. In an attempt to overcome this, Yao et al. switched the potentials of anode and cathode every 20 s to repel adsorbed species from the anode, while limiting the anode potential to maximum 1.2 V and the cathode potential to minimum -1.0 V to prevent side reactions. However, although they mention that switching "provides a certain degree of selectivity", unwanted oxidation of glucose, creatinine and uric acid still occurred [96]. Optimization of the pulse time and applied potentials may further improve selectivity.

4.7. Urea removal efficacy

Besides urea removal with minimal formation of unwanted toxic side products, effective urea removal is important to enable miniaturization of the WAK device. A large range of urea removal rates has been reported in literature ranging from 0.53 to $7.3 \cdot 10^3$ mmol/h/m^2 (median $3.8 \cdot 10^2$ mmol/h/m,^{2} interquartile range $1.3 \cdot 10^2$ to $1.1 \cdot 10^3$ mmol/h/m^2), see Table 1. Therefore, to remove a daily urea production of 240–470 mmol with a daily 8-h dialysis scheme, 0.2–3.6 m^2 of electrode surface is required. By using mesh or nano-structured electrodes, or by folding, dividing or stacking the electrodes, such electrode areas can be easily incorporated into a WAK. Moreover, nano-structuring the electrodes may even improve the catalytic activity of the electrodes [121].

The urea removal rate depends on various parameters. First, it increases with increasing current density since more species in the solution are activated [89,105,110,111]. Second, it increases with increasing urea concentration which results in a faster supply of urea to the electrodes. However, a maximum urea removal rate is reached when urea removal is limited by generation of active chlorine [88,89,110,111]. Third, urea removal is higher at higher temperature, possibly as a result of faster diffusion and thereby faster mixing of urea and active chlorine [108] or due to the increased number of molecules with a kinetic energy higher than the activation energy of the reaction. Keller et al. report 22% lower urea removal at 25 °C *vs* 37 °C [98,100] and others found complete urea removal only above 55 °C [108]. Finally, the cell configuration (electrode pairs in parallel or in series) affects urea removal rates. Koster et al. reported higher removal rates for a parallel configuration of four EO units than for a series configuration with equal net flow, suggesting that a longer residence time within a single EO unit is more efficient than multiple short residences on the same electrodes [92].

4.8. Current efficiency

For application of EO in a WAK, it is important to consider the current efficiency of urea oxidation, because it determines the size and weight of the battery. Current efficiency is defined as the ratio of the current used for urea removal to the total current through the cell. Simka et al. [110,111] observed that higher current densities resulted in lower current efficiencies, probably because at high current density supply of reagents cannot keep up with the current which is consequently wasted on side reactions. On the other hand, higher urea concentrations led to more efficient use of the active chlorine due to a higher probability to react with urea resulting in a higher current efficiency. In principle, there is an optimum current density, where supply of reagent and current are in balance. To enhance supply of urea and improve current efficiency, forced convection near the electrode surface may be applied, for example through stirring or increased flow rates, although this may require additional or larger pumps and higher power consumption, necessitating larger batteries, compromising miniaturization.

5. Urea sorbents

A sorbent that can specifically and efficiently bind urea would be an attractive material for a WAK because, unlike with enzymatic- and electrochemical degradation, no potentially harmful side-products are generated. Urea sorption relies on hydrogen bond formation and dipole interactions or the formation of a covalent bond with urea acting as the nucleophile. Therefore, water, hydrophilic compounds and nitrogen-containing solutes (e.g. creatinine and amino acids) compete for the binding sites of the sorbent. The competition of water molecules cannot be avoided. However, competition of other solutes can be circumvented by placing AC upstream of the urea sorbent, as AC can remove these competing solutes from dialysate. Recent developments have shown
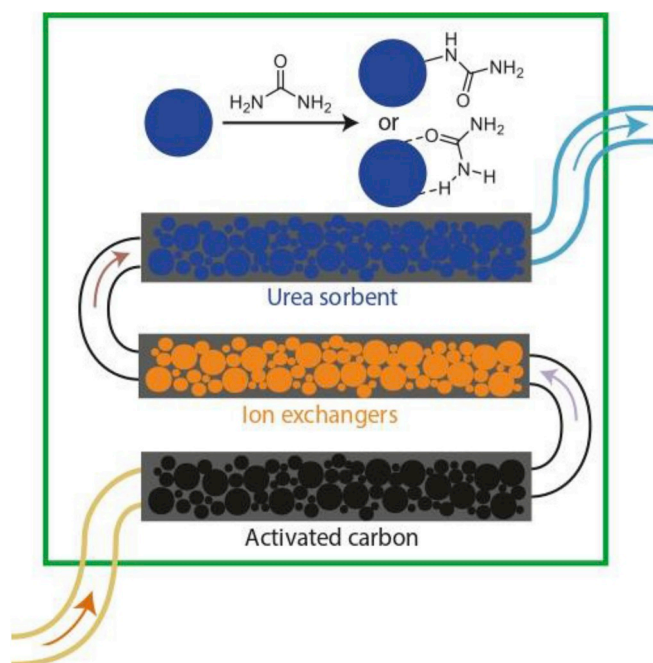
Fig. 5. Schematic representation of a proposed urea sorbent-based WAK. Activated carbon, silica, zeolites and MXenes.

potential of sorbents for effective removal of urea from dialysate, among which AC, silica, zeolites, chitosan, synthetic molecular imprinted polymers (MIPs) and (multi)carbonyl-containing compounds, as discussed in the following sections. A schematic representation of a proposed sorbent-based urea purification unit is shown in Fig. 5.

Sorbents can remove urea from dialysate either by forming covalent or coordination bonds (chemisorption) or by non-covalent bonds (van der Waals forces, dipole interactions and hydrogen bonds, i.e. physisorption). Since urea is uncharged under physiological conditions it is unable to form ionic bonds. In order to remove the daily urea production (240–470 mmol/day) during a 4- to 8-h dialysis session with a reasonable amount of sorbent (<500 g), both high binding capacity and fast sorption kinetics are required. However, urea sorption from

dialysate is difficult because urea and water are both small, polar and weakly nucleophilic molecules [26]. Therefore, a sorbent with affinity for urea based on hydrogen bonds, dipole interactions or electrophilicity, most likely also has affinity for water which is present in the dialysate in a huge molar excess (55 M versus 60 mM for urea at most).

In general, chemisorption is an exothermic and thermally activated process in which non-reversible covalent or coordination bonds are formed with specific functional groups or metal ions present in e.g. a polymeric matrix. However, the kinetics of urea binding to such matrices are relatively slow. In contrast to chemisorption, physisorption is very fast and reversible [122]. Because urea is a very polar molecule, physisorption primarily occurs *via* hydrogen bonding and dipole interactions, resulting in mono- or multilayers on the sorbent's surface [123]. A disadvantage of non-covalent bonding is that sorbent-bound urea is in equilibrium with urea dissolved in the dialysate. The relation between the adsorbed amount and the concentration of urea in solution can be described by the so-called Langmuir isotherm. Since the urea concentration of the dialysate decreases during dialysis, the amount of urea bound per time unit (and thus removed from dialysate) decreases in time. Depending on the type of binding, regeneration of urea sorbents is possible, allowing for re-use of materials.

Urea sorbents are potentially bio-incompatible. For example, AC is hemoincompatible as direct contact with blood, as during charcoal hemoperfusion, is associated with platelet activation and a decrease in platelet and white blood cell count [124,125]. In addition, many urea sorbents have reactive (e.g. carbonyl) groups or may contain toxic compounds (e.g. aluminum in zeolites) as leaching of compounds with aldehydes/carbonyl groups in patients may cause oxidative stress and aluminum may cause bone disease (osteomalacia) [58,59], microcytic anemia [126] and brain damage (encephalopathy) [59]. Hemoincompatibility can be prevented by placing urea sorbents in a dialysate circuit that is separated from blood by a semipermeable membrane that is impermeable for sorbent particles but not for urea. In addition, the biocompatibility of novel urea sorbents has to be evaluated extensively *in vitro* and *in vivo*, including an evaluation of leachables and degradation products, prior to use in humans. To prevent leaching, it is necessary that the sorbent is stable under dialysis conditions and properly washed using validated protocols.

A frequently studied sorbent for urea is activated carbon (AC), a carbonized and chemically activated material with a surface area

Table 2
Binding capacity of activated carbon (AC), silicas, zeolites and MXenes calculated at a urea concentration of 20 mM ($q_{adsorbed}$).

Material	S_{BET} Surface area (m^2/g)	Conditions	Maximum binding capacity q_{max} (mmol/g)	K_L (L/mmol)	$q_{adsorbed}$ at 20 mM urea in mmol/g and ($\mu mol/m^2$)	Reference
Commercial AC (Sigma-Aldrich Co. St. Louis)	978.5	RT*	0.41	0.057	0.22[a] (0.22)	[122]
AC from palm empty fruit bunch	654	RT*	>14.6			[135]
Commercial AC (I-Chem Solution Sdn Bhd)	576	RT*	5.8	0.36[b]	5.1[a] (8.85)	[139]
Commercial AC (Union Carbide Corporation)	n.a.	1 °C **			0.24[c]	[131,132]
Commercial AC (Calgon Carbon 207C)	n.a.	5 °C**			0.18[c]	[130]
Commercial AC (Calgon Carbon 207C)	n.a.	37 °C **			0.10[d]	[130]
Commercial AC (Chemviron type 400)	1050–1200	37 °C *			1.2[e] (1.00–1.14)	[134]
Graphene Oxide	74.8	RT*	0.45	0.040	0.20[a] (2.67)	[122]
Silica (SBA-15)	488	RT*	8.31	0.51[b]	7.6[a] (15.6)	[139]
Silica (Amine-functionalized SBA-15)	158	RT*	9.04	0.67[b]	8.4[a] (53.2)	[139]
Silicalite (SiO$_2$, NH$_4$F and tetrapropylammonium)	n.a.	37 °C *			1.0[e]	[134]
Zeolite ZSM-5 with SiO$_2$:Al$_2$O$_3$ = 23:400	361.3	RT*	0.70	0.019	0.19[a] (0.52)	[122]
Zeolite (Stilbite treated with NaCl)	n.a.	37 °C *			1.1–1.2[e]	[134]
Ti$_3$C$_2$T$_x$ MXenes nanosheets	–	37 °C *	0.27	0.040	0.12[a]	[140]

K_L = Langmuir constant. RT = room temperature. n.a. = not available. q_{max} = maximum binding capacity. $q_{adsorbed}$ = amount of urea adsorbed per gram of sorbent at a certain urea concentration. S_{BET} = surface area per gram of sorbent in m^2/g. *Static conditions. ** Dynamic conditions.
[a] Calculated based on equation (1)
[b] $q_{adsorbed}$ for calculation of K_L was estimated based on Fig. 5 presented in Ref. [139]
[c] estimation based on the concentration dependent formula provided by the authors
[d] estimation based on a comparison with $q_{adsorbed}$ at 5 °C,
[e] $q_{adsorbed}$ at 8 and 41 mM was reported in Ref. [134] and linearly interpolated to $q_{adsorbed}$ at 20 mM.

commonly in the range of 500–1500 m^2/g [127]. Its urea binding capacity has been evaluated under both static (sorbent suspended in an aqueous urea solution) and dynamic (urea solution pumped through a sorbent cartridge) conditions, as summarized in Table 2. To compare binding capacities of different materials, we calculated the amount of urea adsorbed per gram of sorbent ($q_{adsorbed}$, mmol/g) at a dialysate urea concentration of 20 mM (Table 2), a concentration representative for dialysis patients [128]. The amount of urea adsorbed per gram of sorbent was calculated based on the Langmuir adsorption model (equation (1)) [129] or linear correlation [130–132], as appropriate. Studies were excluded if $q_{adsorbed}$ at 20 mM could not be estimated from the available data [22,123,133–138].

$$q_{adsorbed} = q_{max} \frac{K_L[urea]}{1 + K_L[urea]} \qquad (1)$$

Equation (1). K_L = Langmuir constant, q_{max} = maximum binding capacity.

As shown in Table 2, most types of AC have a urea binding capacity of approximately 0.2 mmol/g at equilibrium urea concentration of 20 mM [122,130,138]. Equilibrium is reached within 2 h [122,135,139]. Kim, Lehmann and Giordano showed that urea adsorption by AC increased during "cold dialysis", when the dialysate was cooled to 0–5 °C [130–132,136]. Since adsorption of urea onto AC is exothermic, the desorption of urea from AC is endothermic. Therefore, at lower temperatures the adsorption-desorption equilibrium shifts towards adsorption and $q_{adsorbed}$ thus increased. Another strategy to increase the affinity of AC for urea is to increase the number of oxide functional groups which has been shown to increase the affinity for urea due to H-bonding with the NH_2 group of urea (~0.20 mmol/g versus ~0.07 mmol/g for the un-oxidized AC tested at an equilibrium urea concentration of 40 mM) [141]. However, the urea binding capacity reported was still low (0.20 mmol/g).

Silicon dioxide (SiO_2), also known as silica, has been used as a sorbent for both organic and inorganic compounds. Some forms of silica such as mesoporous SBA-15 (Santa Barbara Amorphous-15) and MCM-41 (Mobil Composition Matter-41) have a high surface area (generally 400–900 m^2/g [142]) and small pores (±10 nm) which make them attractive materials for applications such as waste water treatment and drug delivery [143,144]. Cheah et al. reported a very high $q_{adsorbed}$ for SBA-15 and amine-functionalized SBA-15 (38 mM urea solution in distilled water) of 7.9 and 8.7 mmol/g, respectively [139]. However, the reported $q_{adsorbed}$ for commercial AC that they used as a reference (*i.e.* 5.4 mmol/g at 38 mM urea in distilled water) was much higher than found in other publications, which might be explained by the use of an unvalidated method for urea concentration determination. Although the authors found that functionalization of the mesoporous silica with amines reduced the surface area, q_{max} and $q_{adsorbed}$ increased, possibly because the introduced (protonated) amino groups allowed a better packing of urea molecules on the silica surface *via* hydrogen bonding and/or dipole interactions.

Zeolites are nano porous and crystalline materials mainly consisting of silicium and aluminum oxides. These aluminosilicate networks have an overall negative charge, which is counterbalanced by cations such as Na^+ and K^+ in the lattice. Zeolites are widely used as sorbents and ion-exchangers [145–147]. Cheng et al. investigated Zeolite ZSM-5 for urea sorption and found that q_{max} (0.70 mmol/g) was higher than that of AC (0.41 mmol/g) and graphene oxide (0.45 mmol/g) while $q_{adsorbed}$ was comparable with that of AC and graphene oxide because of the relatively low K_L (0.019 L/mmol compared to 0.057 L/mmol for AC) for ZSM-5 [122]. Wernert et al. tested uremic toxin binding of several zeolites (Linde type A, stilbite, silicalite, mordenite and faujasite) with different physical and chemical properties, among which pore sizes and counter cations [134]. It was found that a smaller pore size did not increase the affinity for urea, but decreased the affinity for other (bigger) solutes instead. Stilbite ($X_n(Si_{27}Al_9)O_{72}·28(H_2O)$) with Na^+ counter ions ($X_n = Na_9$) showed higher affinity for urea than for other

solutes than stilbite with K^+ or Ca^{2+} as counter ions although urea binding capacity of STI-Na (1.1–1.2 mmol/g) was comparable to the binding capacity of AC (1.2 mmol/g) reported in this study. Importantly, aluminum leaching from aluminum-containing zeolites is a potential hazard [122]. The aluminum-free silicalite would therefore be a safer option for application in a WAK, but its urea binding capacity was slightly lower than the binding capacity of AC (1.0 *vs* 1.1–1.2 mmol/g) reported in this study [134]. Overall, mesoporous silicas and zeolites seem to be attractive urea sorbents, although two studies also reported an unlikely high urea sorption capacity for AC (1.0–5.1 mmol/g at a urea concentration of 20 mM) [134,139], putting the reported high values for these sorbents into question.

Recently, two-dimensional (single layer) transition metal carbides with O-, OH- and F- surface terminations (MXenes) have been reported as novel urea sorbents for dialysate regeneration [140]. MXenes are stacked nanosheets with a thickness of ~1 nm per layer and have a size of 1–4 μm. The general formula of these materials is $Ti_3C_2T_x$ in which T_x represents surface groups such as O-, OH- or F- that bind urea *via* hydrogen bonds and dipole interactions. Even though the binding capacity of the reported MXenes for urea is low at 37 °C ($q_{adsorbed}$ = 0.12 mmol/g) the authors state that the fact that these materials bind urea is very promising because MXenes represent a large family of materials with different compositions which can be further explored to identify the best urea sorbent.

5.1. Chitosan-based urea sorbents

Chitosan (CS, Fig. 6), a partially deacetylated polymer of chitin (deacetylation > 50%), is a linear polysaccharide composed of randomly distributed β-1,4-linked D-glucosamine and N-acetyl-D-glucosamine units [148–150]. The amino groups in CS accounts for its sorption capacity due to hydrogen bonds and dipole-interactions with various biomolecules including urea, proteins [151], nucleic acids [152] and cholesterol [153]. CS and its derivatives have many pharmaceutical and biomedical applications, including use in drug delivery systems, tissue engineering, wound dressings and vaccine delivery [154,155].

Table 3 shows the urea binding capacity of CS based urea sorbents. As indicated, the conditions under which the urea binding has been assessed greatly vary between studies, complicating the comparison of chitosan-based materials. Jing et al. utilized CS to stabilize oxycellulose based urea sorbents and developed a membrane consisting of a 90% oxycellulose core and a 10% CS coating with urea binding capacity of 0.14 mmol/g [156]. Even though CS is capable of binding urea *via* hydrogen bonds, the binding capacity is too low for application in a WAK. Therefore, several attempts have been made to improve its binding efficiency [158–162,165,166]. The most frequently studied approach is complexation of CS with metal ions *via* coordinate bonds with the amino groups of CS. It has been shown that urea binds to the unoccupied *d*-orbital of metal ions, among which Cu^{2+} and Zn^{2+} [164],
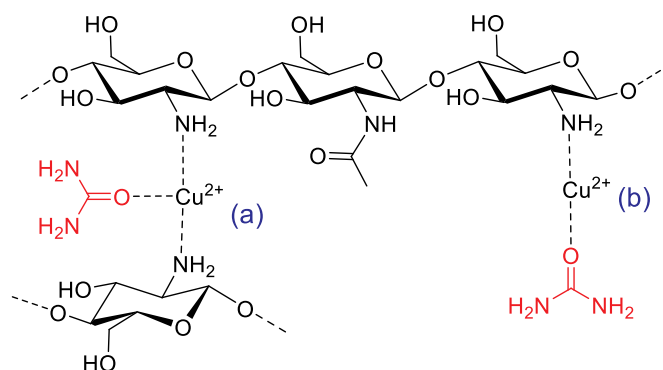
Fig. 6. Coordination model for CS/Cu^{2+}/urea complex, (a) the "bridge model" and (b) the "pendant model".

Table 3
Chitosan (CS) based urea sorbents.

Material	[Urea] (mM) in simulated dialysate	Experimental conditions	Urea binding capacity (mmol/g)	Reference
CS coated dialdehyde cellulose membrane	18.8	pH 7.5 buffer solution, 37 °C, 24 h	0.14	[156]
CS-silk fibroin/Cu^{2+} dense membrane	21.7	pH 7 buffer solution, RT, 8 h	0.3	[157]
CS/Cu^{2+} macroporous membrane	21.7	pH 7 buffer solution, RT, 12 h	1.3	[158]
CS/Cu^{2+} macroporous particles	21.7	pH 6 buffer solution, 37 °C, 8 h	2.0	[159]
CS/Cu^{2+} membrane and particles	20	Physiological fluid, 37 °C, 4 h	0.3–0.4	[160]
CS-magnetite nanocomposites	16.7	Blood serum, 4 h	0.5	[161]
Cross-linked CS/Cu^{2+} copolymer	30	pH 7, RT, 12 h	4.4	[162,163]
Cross-linked CS/Zn^{2+} particle	34.2	Deionized water, RT, 12 h	0.8	[164]

via its oxygen atom (Fig. 6) [167,168]. The coordinate bond is generally an order of magnitude stronger than the hydrogen bond with water, and therefore urea preferentially binds to metal ions. Cu^{2+} has been studied most extensively for urea binding, because it has a relatively high affinity for CS compared with other metal ions (Cu^{2+} ≫ Hg^{2+} > Zn^{2+} > Cd^{2+} > Ni^{2+} > Co^{2+} ~ Ca^{2+}) and, importantly, fabrication of CS/metal ion complexes is a simple process which can be achieved by immersing CS into aqueous solution containing metal ions [149]. Key to obtain a high binding capacity of CS/Cu^{2+} complexes for urea is to increase the Cu^{2+} loading content of CS, which can be achieved by improving accessibility (by applying macroporosity or smaller particles) or by increasing availability of amino groups (by using a crosslinker, see next paragraph). Chen et al. prepared Cu^{2+} loaded CS-silk fibroin blend membranes and observed a urea binding capacity of 0.3 mmol/g at a urea concentration of 22 mM [157]. The fibroin blend membrane was rather dense, which limited the accessibility of amino groups for Cu^{2+} binding. When the accessibility of amino groups was improved by fabricating a macroporous CS membrane with pores of 25–35 μm, the amount of Cu^{2+} loaded in CS increased as compared to the fibroin blend membranes, which resulted in a substantial increase of urea binding capacity from 0.3 to 1.3 mmol/g [158]. In addition to CS/Cu^{2+} complex membranes, CS/Cu^{2+} sorbent particles have also been explored for urea binding [159–161,165]. Zhou et al. [159,165] synthesized CS/Cu^{2+} particles (size not reported) with a pore size of 200 nm and observed a urea binding capacity of 2.0 mmol/g at a urea concentration of 22 mM. Pathak et al. compared urea binding capacities of CS/Cu^{2+} membranes and particles, and found that the urea binding capacities of membranes was slightly lower than that of particles [160]. Furthermore, urea sorption increased with decreasing particle size (0.1, 0.2 and 0.4 mmol/g for particles with diameters of 710, 320 and 297 μm, respectively), which is likely due to the increased surface area and therefore the accessibility of the functional groups in the smaller particles. In another paper, Pathak et al. prepared CS-magnetite (CS–Fe_3O_4) nanocomposite particles with a size of 12–33 nm, by coprecipitation of Fe^{2+} and Fe^{3+} with NaOH in the presence of CS, followed by hydrothermal treatment of the aqueous dispersion from 30 °C to 80 °C for 2 h. The urea binding capacity of the CS-Fe_3O_4 nanoparticles only slightly increased as compared to the larger CS/Cu^{2+} particles (size 297 μm) (0.5 mmol/g *vs* 0.4 mmol/g), probably because the advantage of the larger surface area of the nanoparticles hardly outweighed that of the stronger interaction between Cu^{2+} and urea (than that between Fe^{2+} and Fe^{3+} and urea) [161].

Although the aforementioned studies show that urea binding capacity of CS can be increased by complexation with metal ions, the ability of CS to form complexes with metal ions in water is limited, since most of the amino groups and hydroxyl groups of CS form hydrogen bonds with each other and water molecules, thereby decreasing the number of amino groups available for metal ion complex formation [157,169]. Chen et al. [170] showed that the capacity to form CS-metal ion complexes increased by partially cross-linking the amino groups of CS with glutaraldehyde. Even though part of the amino groups is consumed by the reaction with glutaraldehyde, the cross-linking process prevents remaining amino groups

from forming hydrogen bonds with hydroxyl groups, resulting in an overall higher number of available amino groups for CS-metal ion complex formation [162,164]. Wilson et al. [162] hypothesized that, in addition to the unreacted amino groups of CS, the aldehyde groups originating from glutaraldehyde can also complex Cu^{2+} ions, and they prepared CS/Cu^{2+} complexes by incubating Cu^{2+} ions with glutaraldehyde cross-linked CS. A high urea binding capacity of 4.4 mmol/g was found at a urea concentration of 1–30 mM, however the CS:urea ratio was not specified [162]. This material showed fast urea sorption kinetics at 10 mM urea concentration as equilibrium was reached within 20 min [163]. Of note, the molar ratio of amino groups of CS and aldehydes of glutaraldehyde was 1:2, which means that theoretically all amino groups can be converted into imines.

In conclusion, CS/Cu^{2+} complex sorbents demonstrate high urea binding capacities, especially when glutaraldehyde cross-linking is performed. However, for application in a WAK, potential copper leaching is a major concern. In addition, glutaraldehyde leaching is another safety concern since the imine formed in the reaction between the amino group of CS and glutaraldehyde can be hydrolyzed depending on the pH. Acute and/or chronic toxicity due to Cu^{2+} release may manifest as gastrointestinal symptoms, hemolytic anemia and/or hepato-, neuro- and renal toxicity [171]. Although Zhou et al. [159] and Pathak and Bajpai [160] did not detect Cu^{2+} desorption from CS/Cu^{2+} complex sorbents, safety concerns are an issue for copper ion based urea sorbents.

5.2. Molecular imprinting-based urea sorbents

Molecular imprinting is a relatively novel technique to synthesize a polymer matrix with binding sites complementary to the template molecule (e.g. urea) in terms of shape, size and location of binding units [172–174]. Scheme 1 shows a schematic preparation procedure of a Molecularly Imprinted Polymer (MIP) with specific recognition for the template molecule. Technically, MIP production is rather simple and easy to modulate. Neither complex organic synthesis nor molecule design are required. In general, MIPs show excellent chemical and thermal stability, regenerability, and solvent resistance compared with natural counterparts that also possess specific recognition abilities, such as antibodies [175]. Specific urea recognition is advantageous for a urea sorbent in a WAK to avoid competition by other nitrogenous solutes and prevent adsorption of other beneficial molecules such as amino acids. MIPs are widely used for various applications, such as chromatographic separation [176], sensing [177], drug delivery [178] and catalysis [179].

For the preparation of a MIP (Scheme 1), a reversible complex is first formed between the template and complementary functional monomers *via* covalent and/or non-covalent binding. Subsequently, the complex is co-polymerized with an excess amount of cross-linker, resulting in fixation of the complex in a solid polymer matrix. When the template is removed from the polymerized complex, the geometry and position of the remaining functional groups will be complementary to the template. The imprinting factor is a measure of the imprinting quality, and is defined as the ratio of the binding capacity of imprinted
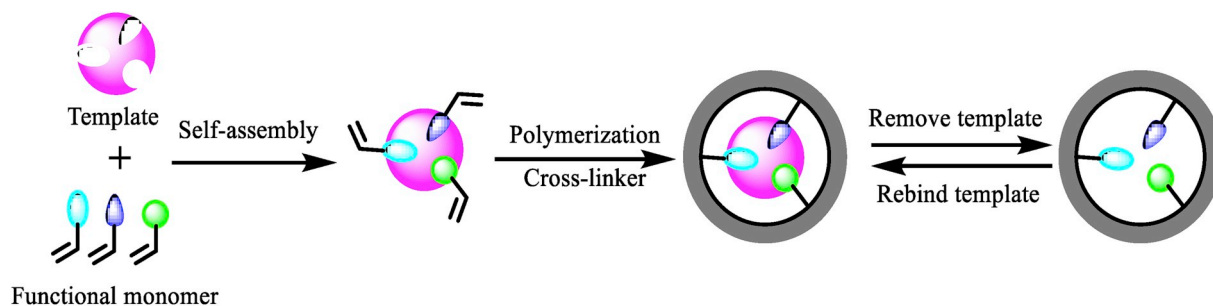
Scheme 1. The formation of template-specific gaps in the polymeric matrix of a molecularly imprinted polymer (MIP).

polymer to that of control (non-imprinted) polymer.

Several attempts have been made to synthesize a urea-imprinted MIP for urea detection or removal [180–188], in which the template recognition is based on hydrogen bonding. Alizadeh et al. synthesized a urea-imprinted MIP using methacrylic acid as functional monomer and ethylene glycol di-methacrylate as cross-linker, all dissolved in acetonitrile. The authors reported a urea binding capacity of 6.3 mmol/g and an imprinting factor of 12.6 in aqueous solution at an unspecified urea concentration [186]. This is a remarkable but questionable finding because the theoretical maximum urea binding capacity of this MIP is only 0.28 mmol/g (assuming that each template molecule added to the mixture provides one imprinting site). Additionally, the carboxylic acid groups, which imprint the sorbent in acetonitrile during the synthesis, are likely protonated during the binding experiment in unbuffered water, but will be deprotonated in a buffered solution (such as dialysate), thereby changing the specific binding. The authors do not comment on both issues, which questions the credibility of this paper.

Macromolecules with suitable functional groups have also been employed to prepare MIPs for urea, even without the addition of a cross-linker [180–185,188]. Huang et al. [188] and Lee et al. [184] evaporated DMSO in which poly(ethylene-co-vinyl alcohol) and urea were dissolved, followed by removal of urea by extraction with ethanol and water, which resulted in the formation of a urea-imprinted MIP membrane. Despite the absence of a cross-linker which normally maintains imprinting site integrity during processing, the MIP membrane demonstrated good imprinting quality with an imprinting factor of 2.3 and a urea binding capacity of 0.4 mmol/g at a urea concentration of 16.7 mM. Also chitosan has been used for the design of a urea-imprinted MIP [180,182,183]. For example, an electrochemical urea sensor was constructed based on MIP films which were prepared by potentiostatic electrodeposition of chitosan onto an Au disk electrode in the presence of urea, followed by removal of urea [183]. The sensor works in a urea concentration range of 10 nM–40 μM but has a very limited urea binding capacity.

5.3. Carbonyl-type sorbents

Carbonyl-type sorbents possess high urea binding capacities and have the ability to form one or two irreversible covalent bonds between their electrophilic carbonyl groups and weakly nucleophilic urea molecules. The electron pair on the nitrogen atom can undergo a nucleophilic attack on the carbonyl group, resulting in a hemi-aminal or imine group (Scheme 2) [189,190]. Because urea is a weak nucleophile, these sorbents lack the selectivity of MIPs and zeolites as the carbonyl groups can also react with other (more reactive) nitrogen containing solutes

present in the dialysate. However, since the urea concentration in the dialysate is much higher than the concentration of competing solutes, such as creatinine and amino acids, and because the sorbents contain urea-reactive groups in excess, the competing solutes may not substantially limit urea removal.

Several urea sorbents that are composed of (crosslinked) polymers with urea-reactive carbonyl groups have been reported in literature such as aldehydes, glyoxaldehydes, ketoesters and ninhydrins (Fig. 7). Carbonyl-based urea sorbents and their binding capacity are shown in Table 4.

Oxidation of alcohol groups in biopolymers such as starch and cellulose using oxidizing agents such as hydrogen peroxide [192], results in aldehyde-containing sorbents with a theoretical maximum aldehyde content and thus urea binding capacity of 4.2 mmol/g if all alcohol groups were oxidized and the aldehyde and urea react in a 1:1 ratio [191]. However, as shown in Table 4, the observed binding capacities of these materials are relatively low: 0.14–0.22 mmol/g [133,191]. This might be due to the fact that urea does not react with the aldehyde, as was observed in a study with ^{14}C-labeled urea [201] and in our own study on the kinetics of urea with a variety of carbonyl groups including aldehydes [202]. In this study, the authors propose that the urea-ammonium/cyanate equilibrium (reaction (1)) shifts when ammonia is bound by the aldehydes in the sorbent and thus urea in fact decomposes [201]. In this case, two aldehyde groups are needed to remove one urea molecule. Moreover, the low urea binding capacities can also be attributed to the slow kinetics of the spontaneous formation of ammonium from urea (reaction (1)). Besides, some oxycelluloses are reported to be unstable in dialysate, as small fragments of the sorbent were formed, which carries the risk of passage through the dialysis membrane into the bloodstream [203]. The low binding capacity and poor stability in dialysate, render these aldehyde-based materials unsuitable as sorbents in a WAK. Recently, Abidin et al. reported oxidized starch nanoparticles containing aldehyde groups with a urea binding capacity of 3.0 mmol/g [192]. The authors proposed that urea forms covalent bonds with the aldehyde groups, but according to the IR spectrum presented and carbonyl content determination assay, the number of carbonyl groups on the oxystarch is too low (0.068 carbonyl groups per 100 glucose units) to remove urea based on covalent binding alone. Similarly, Bing-Lin et al. reported that oxidized epichlorohydrin-cross-linked cyclodextrin reported covalent bonds with urea [193]. They reported a urea binding capacity of 1.1 mmol/g from aqueous solution of pH 7 at 37 °C. However the materials were not characterized with any spectroscopic method. The reported urea removal kinetics of both the work of Abidin et al. [192] and Bing-Lin et al. [193] do not match the typical rate of covalent adsorption and Bing-Lin et al. reported that
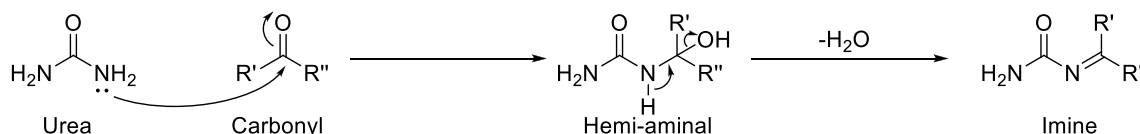
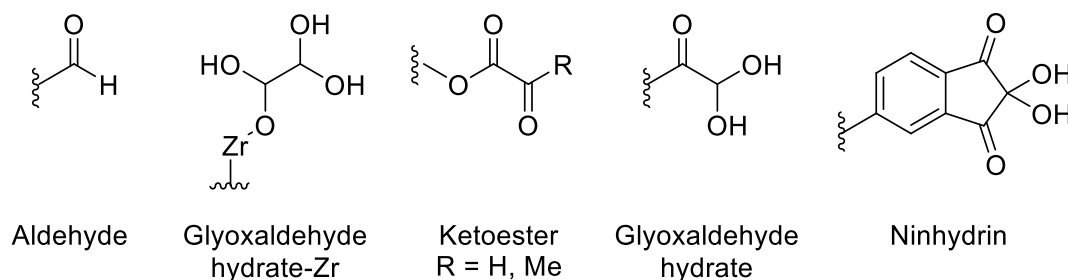**Scheme 2.** General reaction mechanism of urea nitrogen with a carbonyl group.

Fig. 7. Structures of urea-reactive carbonyl groups.

the urea binding capacity increased with an increasing urea concentration. Therefore, we conclude that urea is most likely bound by physisorption [192]. Finally, Eisen filed a patent in which modified poly-vinylalcohol sorbents are claimed containing ketoester moieties with very high and fast urea binding (4.2 mmol/g in 1 h) in a concentrated urea solution (420 mM) at room temperature. However urea binding is not reported at concentrations more relevant to dialysate purification [194].

5.4. Carbonyl-hydrate sorbents

A sorbent with high reactivity towards urea should favorably be very electrophilic. However, highly electrophilic carbonyl groups tend to react with water as a competing nucleophile to form a hydrate. Usually, the carbonyl and its hydrate are in equilibrium in an aqueous environment. However, water has only one nucleophilic site (its oxygen atom), while urea has two (its nitrogen atoms). Therefore, if two or three carbonyl groups are adjacent, for example in indanetrione (**11**) that is in equilibrium with its hydrate ninhydrin (**10**), urea reacts first with the central carbonyl of the triketone (to form intermediate **12**), and then the second nitrogen will form a second intramolecular covalent bond with one of the adjacent carbonyl groups. This results in the formation of a favorable 5-membered ring (**13**), completing the reaction (Scheme 3) [204]. In short, the reaction between water and the carbonyl groups is an equilibrium, whereas the reaction between urea and the carbonyl groups is not and therefore urea will be effectively removed from dialysate.

In a recent publication we reported rate constants (k_2) of urea with low molecular weight hydrated carbonyl compounds under physiological conditions. We found that phenyl glyoxaldehyde and ninhydrin are among the compounds that react fastest with urea (k_2 = 4.1 and 6.8 $M^{-1}h^{-1}$, respectively). Triformylmethane reacted even faster (factor ~23 faster than ninhydrin). Therefore a sorbent in which triformylmethane is incorporated may be very interesting for urea removal from spent dialysate [202].

A drawback of carbonyl-hydrate based sorbents is their relative

complex synthesis. Nevertheless, several carbonyl-hydrate sorbents have been reported. Wong reported a zirconium-glyoxaldehyde complex with a urea binding capacity of 0.45 mmol/g [195]. Kuntz et al. reported a three-step modification of polystyrene to obtain ketoaldehyde hydrate groups [196,197]. Similarly, Poss et al. chemically modified polystyrene to form ketoaldehyde hydrate groups in only two reaction steps, and they reported higher urea binding than the material described by Kuntz (1.5 vs 0.52 mmol/g) (Scheme 4) [198]. Under physiological conditions, ketoaldehyde hydrates are in equilibrium with water and the dehydrated ketoaldehyde group that can form covalent bonds with urea [198].

Similarly, Smakman and Van Doorn modified polystyrene in five steps to form a resin with ninhydrin groups (Scheme 5) [200]. Analogous to the ketoaldehyde-type sorbent presented above, the urea reactive group, indanetrione, is in equilibrium with the ninhydrin group [204]. This ninhydrin-type sorbent showed a maximum binding capacity of 2.0 mmol/g. They also reported that this sorbent bound 1.2 mmol/g from simulated dialysate with a urea concentration of 25–33 mM at 37 °C in 8 h. Furthermore, the material could be sterilized by γ-radiation and did not leach any compounds into the dialysate [199].

5.5. Kinetics of carbonyl-type urea sorbents

Carbonyl-type urea sorbents are characterized by relatively slow urea sorption [191]. For this reason, it usually takes several days before the maximum binding capacity is reached at 37 °C. As the covalent binding of urea is a thermally activated process, the reaction rate increases at higher temperatures. Smakman and Van Doorn monitored urea sorption at several temperatures over time and found that at 37 °C 0.75 mmol of urea per gram sorbent was bound after 4 h, after which the rate of urea sorption decreased but sorption continued beyond 20 h. This implies that ~300–600 g of this material is needed to remove the daily production of urea (240–470 mmol) in a 4 h dialysis session at 37 °C. Interestingly at 80 °C, the maximum binding capacity (2.0 mmol/g) was almost reached after 4 h, but unfortunately this is not an option

Table 4
Covalent urea sorbents reported in literature.

Polymer matrix	Appearance	Urea-reactive group	Urea-reactive groups available (mmol/g)	Reported urea binding capacity (mmol/g)	Reference
Oxystarch	Gel	Aldehyde	0.62–4.2	0.14–0.20[a]	[191]
Oxycellulose	Gel	Aldehyde	n.a.	0.13–0.22	[133]
Oxystarch	Particles	Aldehyde	n.a.	3.0	[192]
Oxidized crosslinked cyclodextran	Particles	Aldehyde	4.5	1.1	[193]
Glyoxylic ester-PVA	Gum	Ketoester	n.a.	0.01–4.2	[194]
Zr/glyoxal complex	Immobilized on AC or on Zirconium sorbent	Glyoxaldehyde (hydrate)	0.52–1.1	0.20–0.45	[195]
Modified PS	Linear polymer	Glyoxaldehyde (hydrate)	3.8–4.0	0.52	[196,197]
Modified PS-DVB copolymer	Macroporous beads	Glyoxaldehyde (hydrate)	3.1–3.6	1.5	[198]
Modified PS-DVB copolymer	Macroporous beads	Indanetrione (ninhydrin)	>2.7 [199]	1.1–2.0	[200]

[a] Over the first 24 h.
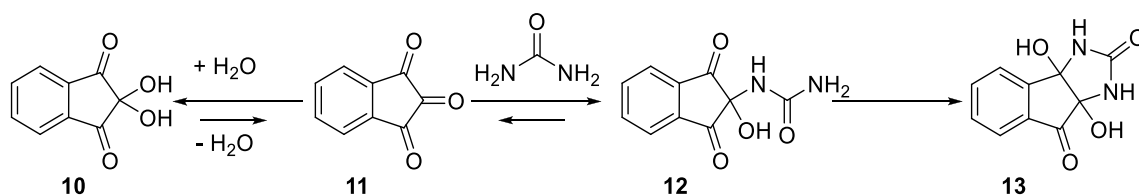
Scheme 3. The reaction of urea with vicinal ketones.
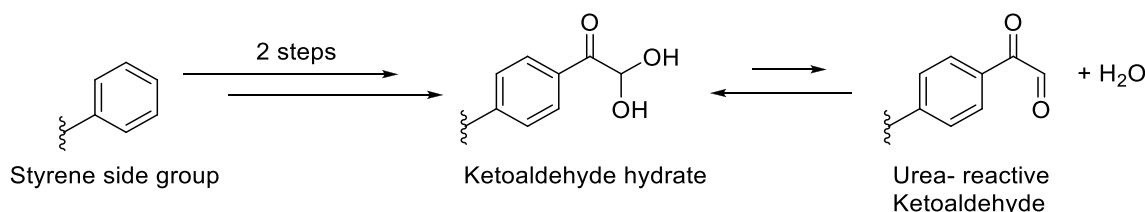
Scheme 4. Synthetic route towards ketoaldehyde-hydrate-type sorbent and its equilibrium with water.

in a WAK [199]. In addition, carbonyl-based sorbents are not selective towards urea because they will react faster with more nucleophilic compounds present in the dialysate (such as creatinine and amino acids). These solutes can be prevented from entering the urea-sorbent column by placing AC upstream of the urea sorbent column.

6. Conclusions and perspectives

The greatest challenge in the development of a WAK is the development of an efficient urea removal technology. Enzymatic hydrolysis, electrochemical decomposition, physisorption and chemisorption have been explored, but all of these methods have disadvantages. A summary of the urea removal strategies and their advantages and disadvantages is given in Table 5.

Urease for enzymatic hydrolysis of urea followed by ammonium adsorption by a cation-exchanger is currently the most efficient and effective method to remove urea from dialysate. A relatively small amount of enzyme immobilized on a substrate (30–50 g) is required to convert the daily urea production into ammonium and bicarbonate. Even though bicarbonate formation is an advantage as it may correct for metabolic acidosis, a urease-based urea removal system is associated with some major disadvantages: (1) the need for a relatively large amount of zirconium phosphate to remove ammonium ions, (2) risk of early sorbent exhaustion resulting in release of toxic ammonium into the patient (3) binding of other cations (i.e. calcium, magnesium and potassium), requiring replenishment of these cations from a separate reservoir, and (4) sodium release which complicates fluid management. Overall, urea removal by enzymatic hydrolysis is effective and offers prospects for a portable artificial kidney, but all elements required to overcome the existing disadvantages of this method make it very difficult to reduce the size of the device to wearable proportions without the need for frequent change of disposables.

Urea removal by electro-oxidation seems promising, but significant challenges remain. First of all, the selectivity has to be ensured to minimize generation of harmful side-products and undesired oxidation of important dialysate components. Options for improving selectivity

include optimization of the electrode material, functionalization of the electrode with catalytic groups or selective membranes and pulsed-potential techniques. Furthermore, a trade-off between efficacy and current efficiency (the fraction of the current used for urea removal) will have to be made. Increasing the electrode area and/or area to volume ratio will have positive effects on both the efficacy and the efficiency. Moreover, forced convection may further improve both. Increased current density to improve efficacy is not a good approach, as this increases formation of toxic side-products and reduces efficiency. Alternatively, a potential driven approach can be implemented, which should reduce side-products and increase efficiency. However, complete avoidance of side-products will be challenging due to the relatively high oxidation potential of urea and primary dependence on indirect oxidation. This will require strategies to reduce the supply of other readily oxidizable substances to the electrodes and to remove side-products downstream of the electrodes (e.g. by applying activated carbon up- and downstream of the electrodes, respectively).

An applicable urea sorbent with high specificity, high binding capacity and fast kinetics that does not release toxic side products, is not yet available. The affinity for urea of AC and zeolites is still too low to allow for application in a wearable device. Future studies might yield urea-specific zeolites or modified AC with high affinity and binding capacity. Urea sorption on silica shows high urea binding capacities, but needs to be validated to evaluate the true potential of this material for incorporation in a WAK.

(Glutaraldehyde-crosslinked) CS/Cu^{2+} complex sorbents show high urea binding capacity. However, potential copper leaching is a substantial concern for application in a WAK.

A urea-imprinted MIP seems appealing because of its potential specificity for urea. However, molecular imprinting technology for the synthesis of a urea sorbent is still at a very early stage. MIP-based urea sorbents have been developed for urea detection, but only a few studies focused on urea binding for dialysate regeneration. Furthermore, available urea-imprinted MIPs are based on hydrogen bond interaction, which poses the problem of competitive binding by water. Another possible drawback of MIP based urea sorbents is that a substantial
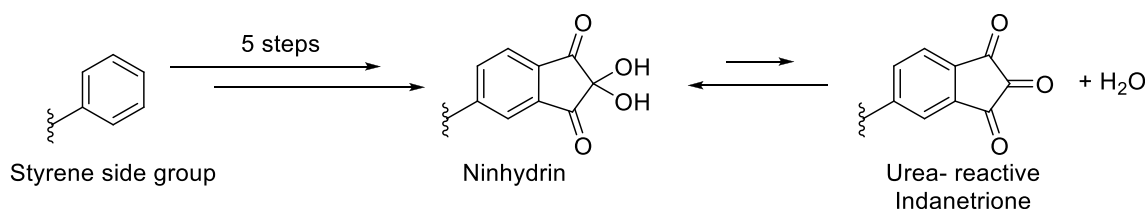
Scheme 5. Synthetic route towards ninhydrin-type sorbent and its equilibrium with water.

Table 5

Overview of urea removal strategies.

Method	Selectivity	Toxic by-product	Urea removal capacity	Urea removal rate	Remarks
Enzymatic hydrolysis	+ + +	Ammonium	+ + +	+ + +	Large amount of cation-exchanger, strategy for limiting sodium release and specific storage conditions needed.
Electrochemical decomposition	–	Oxidation products	+	+	Biocompatibility issues, AC required to remove oxidation products.
Physisorption	–	None[a]	–	+ +	Competition with water.
Chemisorption	–	None[a]	+	–	Complex syntheses of sorbent

[a] Leaching of substances should be excluded. AC = activated carbon.

amount of "nonfunctional" cross-linker is required to maintain the MIP structure, which decreases the maximum binding capacity. Alternative imprinting strategies such as covalent or coordination imprinting are potentially suitable and need further exploration.

Carbonyl-hydrate urea sorbents seem promising for application in a WAK as (1) they are capable of removing urea from dialysate without releasing potentially harmful side-products and (2) a relatively small amount of sorbent (300–600 g of ninhydrin-type sorbents) would suffice to remove the daily urea production of 240–470 mmol. However, a limitation of carbonyl-type sorbents is the slow adsorption kinetics under physiological conditions. Urea sorption is fastest within the first hours but insufficient (max. 0.75 mmol/g in 4 h), which would significantly increase the amount of sorbent beyond the acceptable limit for a wearable device. Further research should focus on a covalent urea sorbent with a higher binding capacity and faster kinetics. Another issue of the carbonyl-hydrate sorbent is the low specificity for urea. Urea is a very weak nucleophile, so stronger nucleophiles such as amino acids and creatinine would most likely also react with these sorbents, thereby reducing the number of potential binding sites for urea. This might be circumvented by placing AC upstream of the sorbent to remove these components before they pass the urea sorbent.

In conclusion, none of the currently available urea removal methods make a truly wearable dialysis devices feasible at present. However, a portable dialysate regeneration system seems within reach in the near future. Several technological developments in the different urea removal strategies may enable realization of a light-weight WAK in the more distant future.

Data availability

The data reported in this review can be retrieved from the original papers as cited in the text.

Acknowledgements

References

[1] Fresenius Medical Care (FMC), Annual Report 2018. [ONLINE] Retrieved from: https://www.freseniusmedicalcare.com/fileadmin/data/com/pdf/Media_Center/Publications/Annual_Reports/FME_Annual-Report_2018.pdf , Accessed date: 11 July 2019.

[2] United States Renal Data System (USRDS), [ONLINE] Retrieved from: http://www.usrds.org/2015/view/v2_07.aspx.

[3] M. Coemans, C. Susal, B. Dohler, D. Anglicheau, M. Giral, O. Bestard, C. Legendre, M.P. Emonds, D. Kuypers, G. Molenberghs, G. Verbeke, M. Naesens, Analyses of the short- and long-term graft survival after kidney transplantation in Europe between 1986 and 2015, Kidney Int. 94 (5) (2018) 964–973.

[4] N.J.H. Broers, R.J.H. Martens, B. Canaud, T. Cornelis, T. Dejagere, N.M.P. Diederen, M.M.H. Hermans, C. Konings, F. Stifft, J. Wirtz, K.M.L. Leunissen, F.M. van der Sande, J.P. Kooman, Health-related quality of life in end-stage renal disease patients: the effects of starting dialysis in the first year after the transition period, Int. Urol. Nephrol. 50 (6) (2018) 1131–1142.

[5] Fresenius Medical Care (FMC), Annual Report 2016. [ONLINE] Retrieved from: https://www.freseniusmedicalcare.com/fileadmin/data/com/pdf/investors/News__Publications/Annual_Reports/2016/FMC_AnnualReport_2016_en.pdf , Accessed date: 30 October 2017.

[6] R. Vanholder, A. Pletinck, E. Schepers, G. Glorieux, Biochemical and clinical impact of organic uremic retention solutes: a comprehensive update, Toxins 10 (1) (2018).

[7] J. Susel, A. Batycka-Baran, A. Reich, J.C. Szepietowski, Uraemic pruritus markedly affects the quality of life and depressive symptoms in haemodialysis patients with end-stage renal disease, Acta Derm. Venereol. 94 (3) (2014) 276–281.

[8] C. Zoccali, U. Moissl, C. Chazot, F. Mallamaci, G. Tripepi, O. Arkossy, P. Wabel, S. Stuard, Chronic fluid overload and mortality in ESRD, J. Am. Soc. Nephrol. 28 (8) (2017) 2491–2497.

[9] K. Kalantar-Zadeh, A.R. Tortorici, J.L. Chen, M. Kamgar, W.L. Lau, H. Moradi, C.M. Rhee, E. Streja, C.P. Kovesdy, Dietary restrictions in dialysis patients: is there anything left to eat? Semin. Dial. 28 (2) (2015) 159–168.

[10] L.F. Silva, G.B. Lopes, T.O. Cunha, B.M. Protasio, R.L. Pisoni, S.A. James, A.A. Lopes, Coping with fluid restriction and the quality of life in hemodialysis patients with very low or no daily urine output, Int. J. Artif. Organs 37 (6) (2014) 427–435.

[11] P. Evenepoel, B.K. Meijers, B. Bammens, L. Viaene, K. Claes, B. Sprangers, M. Naesens, T. Hoekstra, G. Schlieper, D. Vanderschueren, D. Kuypers, Phosphorus metabolism in peritoneal dialysis- and haemodialysis-treated patients, Nephrol. Dial. Transplant. 31 (9) (2016) 1508–1514.

[12] S. Mujais, K. Story, Peritoneal dialysis in the US: evaluation of outcomes in contemporary cohorts, Kidney Int. Suppl. (103) (2006) S21–S26.

[13] C. Kotsokalis, FP7-248261 periodic report Nephron+, (2011) (Unpublished report).

[14] International Society of Peritoneal Dialysis (ISPD), Questions about PD, (2013) [ONLINE]. Retrieved from: https://ispd.org/question/what-is-the-rule-of-thumb-when-advising-a-patient-about-lifting-restrictions/ , Accessed date: 19 June 2019.

[15] M.V. Rocco, R.S. Lockridge Jr., G.J. Beck, P.W. Eggers, J.J. Gassman, T. Greene, B. Larive, C.T. Chan, G.M. Chertow, M. Copland, C.D. Hoy, R.M. Lindsay, N.W. Levin, D.B. Ornt, A. Pierratos, M.F. Pipkin, S. Rajagopalan, J.B. Stokes, M.L. Unruh, R.A. Star, A.S. Kliger, G. Frequent Hemodialysis Network Trial, A. Kliger, P. Eggers, J. Briggs, T. Hostetter, A. Narva, R. Star, B. Augustine, P. Mohr, G. Beck, Z. Fu, J. Gassman, T. Greene, J. Daugirdas, L. Hunsicker, B. Larive, M. Li, J. Mackrell, K. Wiggins, S. Sherer, B. Weiss, S. Rajagopalan, J. Sanz, S. Dellagrottaglie, M. Kariisa, T. Tran, J. West, M. Unruh, R. Keene, J. Schlarb, C. Chan, M. McGrath-Chong, R. Frome, H. Higgins, S. Ke, O. Mandaci, C. Owens, C. Snell, G. Eknoyan, L. Appel, A. Cheung, A. Derse, C. Kramer, N. Geller, R. Grimm, L. Henderson, S. Prichard, E. Roecker, M. Rocco, B. Miller, J. Riley, R. Schuessler, R. Lockridge, M. Pipkin, C. Peterson, C. Hoy, A. Fensterer, D. Steigerwald, J. Stokes, D. Somers, A. Hilkin, K. Lilli, W. Wallace, B. Franzwa, E. Waterman, C. Chan, M. McGrath-Chong, M. Copland, A. Levin, L. Sioson, E. Cabezon, S. Kwan, D. Roger, R. Lindsay, R. Suri, J. Champagne, R. Bullas, A. Garg, A. Mazzorato, E. Spanner, M. Rocco, J. Burkart, S. Moossavi, V. Mauck, T. Kaufman, A. Pierratos, W. Chan, K. Regozo, S. Kwok, The effects of frequent nocturnal home hemodialysis: the frequent hemodialysis network nocturnal trial, Kidney Int. 80 (10) (2011) 1080–1091.

[16] G.M. Chertow, N.W. Levin, G.J. Beck, T.A. Depner, P.W. Eggers, J.J. Gassman, I. Gorodetskaya, T. Greene, S. James, B. Larive, R.M. Lindsay, R.L. Mehta, B. Miller, D.B. Ornt, S. Rajagopalan, A. Rastogi, M.V. Rocco, B. Schiller,

O. Sergeyeva, G. Schulman, G.O. Ting, M.L. Unruh, R.A. Star, A.S. Kliger, In-center hemodialysis six times per week versus three times per week, N. Engl. J. Med. 363 (24) (2010) 2287–2300.

[17] B.F. Culleton, M. Walsh, S.W. Klarenbach, G. Mortis, N. Scott-Douglas, R.R. Quinn, M. Tonelli, S. Donnelly, M.G. Friedrich, A. Kumar, H. Mahallati, B.R. Hemmelgarn, B.J. Manns, Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial, Jama 298 (11) (2007) 1291–1299.

[18] M.J. Jardine, L. Zuo, N.A. Gray, J.R. de Zoysa, C.T. Chan, M.P. Gallagher, H. Monaghan, S.M. Grieve, R. Puranik, H. Lin, J.M. Eris, L. Zhang, J. Xu, K. Howard, S. Lo, A. Cass, V. Perkovic, A trial of extending hemodialysis hours and quality of life, J. Am. Soc. Nephrol. 28 (6) (2017) 1898–1911.

[19] A. Mathew, J.A. McLeggon, N. Mehta, S. Leung, V. Barta, T. McGinn, G. Nesrallah, Mortality and hospitalizations in intensive dialysis: a systematic review and meta-analysis, Can. J. Kidney Health Dis. 5 (2018) 2054358117749531.

[20] J.W. Agar, Review: understanding sorbent dialysis systems, Nephrology 15 (4) (2010) 406–411.

[21] S.R. Ash, Sorbents in treatment of uremia: a short history and a great future, Semin. Dial. 22 (6) (2009) 615–622.

[22] H. Yatzidis, A convenient haemoperfusion micro-apparatus for treatment of endegeneous and exogenous intoxicatons; its use as an effective artificial kidney, Proc. Eur. Dial. Transpl. Assoc. 1 (1964) 83–87.

[23] J.C. Bock, A study of a decolorizing carbon, J. Am. Chem. Soc. 42 (1920) 1564–1569.

[24] I.D. Weiner, W.E. Mitch, J.M. Sands, Urea and ammonia metabolism and the control of renal nitrogen excretion, Clin. J. Am. Soc. Nephrol. 10 (8) (2015) 1444–1458.

[25] C.S. Shinaberger, R.D. Kilpatrick, D.L. Regidor, C.J. McAllister, S. Greenland, J.D. Kopple, K. Kalantar-Zadeh, Longitudinal associations between dietary protein intake and survival in hemodialysis patients, Am. J. Kidney Dis. 48 (1) (2006) 37–49.

[26] H.D. Lehmann, R. Marten, C.A. Gullberg, How to catch urea? Considerations on urea removal from hemofiltrate, Artif. Organs 5 (3) (1981) 278–285.

[27] J.L. Deignan, S.D. Cederbaum, W.W. Grody, Contrasting features of urea cycle disorders in human patients and knockout mouse models, Mol. Genet. Metab. 93 (1) (2008) 7–14.

[28] P.S. Francis, S.W. Lewis, K.F. Lim, Analytical methodology for the determination of urea: current practice and future trends, Trac. Trends Anal. Chem. 21 (5) (2002) 389–400.

[29] R. Vanholder, T. Gryp, G. Glorieux, Urea and chronic kidney disease: the comeback of the century? (in uraemia research), Nephrol. Dial. Transplant. 33 (1) (2018) 4–12.

[31] P. Dirnhuber, F. Schutz, The isomeric transformation of urea into ammonium cyanate in aqueous solutions, Biochem. J. 42 (4) (1948) 628–632.

[32] L.R. Singh, T.A. Dar, F. Ahmad, Living with urea stress, J. Bio Sci. 34 (2) (2009) 321–331.

[33] S. Sun, J.Y. Zhou, W. Yang, H. Zhang, Inhibition of protein carbamylation in urea solution using ammonium-containing buffers, Anal. Biochem. 446 (2014) 76–81.

[34] B. Krajewska, Ureases I. Functional, catalytic and kinetic properties: a review, J. Mol. Catal. B Enzym. 59 (1–3) (2009) 9–21.

[35] B. Krajewska, Ureases. II. Properties and their customizing by enzyme immobilizations: a review, J. Mol. Catal. B Enzym. 59 (1–3) (2009) 22–40.

[36] C. Follmer, F.V. Pereira, N.P. Da Silveira, C.R. Carlini, Jack bean urease (EC 3.5.1.5) aggregation monitored by dynamic and static light scattering, Biophys. Chem. 111 (1) (2004) 79–87.

[37] W.H.R. Shaw, D.G. Walker, Kinetic studies of thiourea derivatives. IV. The methylated thioureas. Conclusions, J. Am. Chem. Soc. 80 (20) (1958) 5337–5342.

[38] W.H.R. Shaw, J.J. Bordeaux, The decomposition of urea in aqueous media, J. Am. Chem. Soc. 77 (18) (1955) 4729–4733.

[39] B.P. Callahan, Y. Yuan, R. Wolfenden, The burden borne by urease, J. Am. Chem. Soc. 127 (31) (2005) 10828–10829.

[40] M. Yao, X. Chen, C.G. Zhan, Reaction pathway and free energy barrier for urea elimination in aqueous solution, Chem. Phys. Lett. 625 (2015) 143–146.

[41] M. Yao, W. Tu, X. Chen, C.G. Zhan, Reaction pathways and free energy profiles for spontaneous hydrolysis of urea and tetramethylurea: unexpected substituent effects, Org. Biomol. Chem. 11 (43) (2013) 7595–7605.

[42] M. Roberts, The regenerative dialysis (REDY) sorbent system, Nephrology 4 (4) (1998) 275–278.

[43] M. Gordon, M. Popovtzer, M. Greenbaum, M. McArthur, J.R. De Palma, H. Maxwell, Zirconium phosphate-A potentially useful adsorbent in the treatment of chronic uremia, Proc. Eur. Dial. Transpl. Assoc. 5 (1968) 86.

[44] J.P. Chen, S.H. Chiu, Preparation and characterization of urease immobilized onto porous chitosan beads for urea hydrolysis, Bioprocess Eng. 21 (4) (1999) 323–330.

[45] J. Chen, S. Chiu, A poly(N-isopropylacrylamide-co-N-acryloxysuccinimide-co-2-hydroxyethyl methacrylate) composite hydrogel membrane for urease immobilization to enhance urea hydrolysis rate by temperature swing, Enzym. Microb. Technol. 26 (5–6) (2000) 359–367.

[46] C.C. Lin, M.C. Yang, Urea permeation and hydrolysis through hollow fiber dialyzer immobilized with urease: storage and operation properties, Biomaterials 24 (11) (2003) 1989–1994.

[47] M.C. Yang, C.C. Lin, Urea permeation and hydrolysis through hollow fiber dialyzer immobilized with urease, Biomaterials 22 (9) (2001) 891–896.

[48] F. Kara, G. Demirel, H. Tumturk, Immobilization of urease by using chitosan-alginate and poly(acrylamide-co-acrylic acid)/kappa-carrageenan supports, Bioproc. Biosyst. Eng. 29 (3) (2006) 207–211.

[49] S. Rejikumar, S. Devi, Preparation and characterization of urease bound on crosslinked poly(vinyl alcohol), J. Mol. Catal. B Enzym. 4 (1–2) (1998) 61–66.

[50] P.K. Srivastava, A.M. Kayastha, R. Srinivasan, Characterization of gelatin-immobilized pigeonpea urease and preparation of a new urea biosensor, Biotechnol. Appl. Biochem. 34 (Pt 1) (2001) 55–62.

[51] N. Bortone, M. Fidaleo, M. Moresi, Immobilization/stabilization of acid urease on Eupergit(R) supports, Biotechnol. Prog. 28 (5) (2012) 1232–1244.

[52] M. Monier, A.M. El-Sokkary, Modification and characterization of cellulosic cotton fibers for efficient immobilization of urease, Int. J. Biol. Macromol. 51 (1–2) (2012) 18–24.

[53] L. Wang, S. Wang, X.Y. Deng, Y.C. Zhang, C.R. Xiong, Development of coconut shell activated carbon-tethered urease for degradation of urea in a packed bed, Acs Sustain. Chem. Eng. 2 (3) (2014) 433–439.

[54] G.D. Kibarer, G. Akovali, Optimization studies on the features of an activated charcoal-supported urease system, Biomaterials 17 (15) (1996) 1473–1479.

[55] M.J. Blumenkrantz, A. Gordon, M. Roberts, A.J. Lewin, E.A. Pecker, J.K. Moran, J.W. Coburn, M.H. Maxwell, Applications of the Redy sorbent system to hemodialysis and peritoneal dialysis, Artif. Organs 3 (3) (1979) 230–236.

[56] Association for the Advancement of Medical Instrumentation (AAMI), Sorbent-based regenerative hemodialysis systems, AAMI TIR77 (2018).

[57] N.H. Lameire, C. Ronco (Eds.), Dialysis, Dialyzers and Sorbents. Where Are We Going? Karger Medical and Scientific Publishers, Basel, 2001, pp. 140–153.

[58] C. Mion, B. Branger, R. Issautier, H.A. Ellis, M. Rodier, S. Shaldon, Dialysis fracturing osteomalacia without hyperparathyroidism in patients treated with HCO3 rinsed Redy cartridge, Trans. Am. Soc. Artif. Intern. Organs 27 (1981) 634–638.

[59] A.M. Pierides, P.P. Frohnert, Aluminum related dialysis osteomalacia and dementia after prolonged use of the Redy cartridge, Trans. Am. Soc. Artif. Intern. Organs 27 (1981) 629–633.

[60] A.M. Pierides, M.P. Myli, Iron and aluminum osteomalacia in hemodialysis patients, N. Engl. J. Med. 310 (5) (1984) 323.

[61] P.J. Drury, G.A. Harston, P.R. Ineson, S. Smith, J.L. Stoves, C.S. Bray, M.M. Black, Aluminum release from the sorbsystem D-3160 and D-3260 cartridges, Life Support Syst. 4 (3) (1986) 211–219.

[62] R.L. McGill, J.R. Bakos, T. Ko, S.E. Sandroni, R.J. Marcus, Sorbent hemodialysis: clinical experience with new sorbent cartridges and hemodialyzers, Am. Soc. Artif. Intern. Organs J. 54 (6) (2008) 618–621.

[63] W.B. Shapiro, The current status of sorbent hemodialysis, Semin. Dial. 4 (1) (1991) 40–45.

[64] W. Drukker, F.M. Parsons, A. Gordon, Practical Application of Dialysis Fluid Regeneration: the REDY System, in: W. Drukker, F.M. Parsons, J.F. Maher (Eds.), Replacement of Renal Function by Dialysis, Springer, 1979, pp. p244–p258.

[65] J.D. Sherman, D.S. Bem, G.J. Lewis, Process for Removing Toxins from Bodily Fluids Using Zirconium or Titanium Microporous Compositions, US, 2001.

[66] A.S. De Vriese, M. Langlois, D. Bernard, I. Geerolf, L. Stevens, J.R. Boelaert, M. Schurgers, E. Matthys, Effect of dialyser membrane pore size on plasma homocysteine levels in haemodialysis patients, Nephrol. Dial. Transplant. 18 (12) (2003) 2596–2600.

[67] T.A. Ikizler, J.H. Greene, M. Yenicesu, G. Schulman, R.L. Wingard, R.M. Hakim, Nitrogen balance in hospitalized chronic hemodialysis patients, Kidney Int. Suppl. 57 (1996) S53–S56.

[68] S. Dasarathy, R.P. Mookerjee, V. Rackayova, V. Rangroo Thrane, B. Vairappan, P. Ott, C.F. Rose, Ammonia toxicity: from head to toe? Metab. Brain Dis. 32 (2) (2017) 529–538.

[69] V. Gura, M.B. Rivara, S. Bieber, R. Munshi, N.C. Smith, L. Linke, J. Kundzins, M. Beizai, C. Ezon, L. Kessler, J. Himmelfarb, A wearable artificial kidney for patients with end-stage renal disease, JCI Insight 1 (8) (2016) 15.

[70] A. Davenport, Dialysis: a wearable dialysis device: the first step to continuous therapy, Nat. Rev. Nephrol. 12 (9) (2016) 512–514.

[71] J. Munoz Mendoza, R. Arramreddy, B. Schiller, Dialysate sodium: choosing the optimal hemodialysis bath, Am. J. Kidney Dis. 66 (4) (2015) 710–720.

[72] A.M. Pierides, W.G. Edwards Jr., U.X. Cullum Jr., J.T. McCall, H.A. Ellis, Hemodialysis encephalopathy with osteomalacic fractures and muscle weakness, Kidney Int. 18 (1) (1980) 115–124.

[73] M.K. Ward, A.M. Pierides, P. Fawcett, D.A. Shaw, R.H. Perry, B.E. Tomlinson, D.N.S. Kerr, Dialysis encephalopathy syndrome, Proc. Eur. Dial. Transpl. Assoc. 13 (1976) 348.

[74] F. Llach, P.W. Gardner, C.R. George, O. Cairoli, Aluminum kinetics using bicarbonate dialysate with the sorbent system, Kidney Int. 43 (4) (1993) 899–902.

[75] Association for the Advancement of Medical Instrumentation (AAMI), Hemodialysis systems, ANSI/AAMI RD 5 (1981).

[76] M.K. van Gelder, S.M. Mihaila, J. Jansen, M. Wester, M.C. Verhaar, J.A. Joles, D. Stamatialis, R. Masereeuw, K.G.F. Gerritsen, From portable dialysis to a bioengineered kidney, Expert Rev. Med. Devices 15 (5) (2018) 323–336.

[77] A. Davenport, V. Gura, C. Ronco, M. Beizai, C. Ezon, E. Rambod, A wearable haemodialysis device for patients with end-stage renal failure: a pilot study, Lancet 370 (9604) (2007) 2005–2010.

[78] W. Lornoy, I. Becaus, J.M. Billiouw, L. Sierens, P. Van Malderen, P. D'Haenens, On-line haemodiafiltration. Remarkable removal of beta2-microglobulin. Long-term clinical observations, Nephrol. Dial. Transplant. 15 (Suppl 1) (2000) 49–54.

[79] A automated wearable artificial kidney (AWAK). [ONLINE]. Retrieved from: http://awak.com/product/ , Accessed date: 30 December 2018.

[80] H. Htay, S. Gow, M. Jayaballa, E. Oei, S.N.H. Jamaluddin, J. Lim, M. Foo, Evaluation of Safety of Automated Wearable Artificial Kidney (AWAK) Device in PD Patients [poster], ISN WCN19-0817 Melbourne, Australia, 2019.

[81] W.K. Lo, J.M. Bargman, J. Burkart, R.T. Krediet, C. Pollock, H. Kawanishi, P.G. Blake, Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis, Perit. Dial. Int. 26 (5) (2006) 520–522.

[82] EasyDial, [ONLINE]. Retrieved from: http://easydialhdbs.com/ , Accessed date: 11 July 2019.

[83] T. McNamara, O. Khawar, S. Foster, In-vitro Dialysis Clearances Uing Darma, the EasyDial Portable Hemodialysis Machine, ASN FR-PO825, 2017 [abstract].

[84] National Institute of Diabetes and Kidney Diseases (NIH), Hemodialysis dose & adequacy, [ONLINE]. Retrieved from: https://www.niddk.nih.gov/health-information/kidney-disease/kidney-failure/hemodialysis/dose-adequacy , Accessed date: 11 July 2019.

[85] Diality. [ONLINE]. Retrieved from: https://www.diality.com/ , Accessed date: 11 July 2019.

[86] O. Khawar, T. McNamara, S. Foster, In-vitro Dialysate Regeneration Using Dharma, the EasyDial Portable Hemodialysis Machine, ASN SA-PO758, 2017 [abstract].

[87] S.B. Tuwiner, Research, Design, and Development of an Improved Water Reclamation System for Manned Space Vehicles, RAI Research Corp, 1966 Report 364 for NASA Contract NASA-4373.

[88] M. Wester, M.K. van Gelder, J.A. Joles, F. Simonis, D.H.M. Hazenbrink, T.W.M. van Berkel, K.R.D. Vaessen, W.H. Boer, M.C. Verhaar, K.G.F. Gerritsen, Removal of urea by electro-oxidation in a miniature dialysis device: a study in awake goats, Am. J. Physiol. Renal. Physiol. 315 (5) (2018) F1385–F1397.

[89] M. Wester, F. Simonis, N. Lachkar, W.K. Wodzig, F.J. Meuwissen, J.P. Kooman, W.H. Boer, J.A. Joles, K.G. Gerritsen, Removal of urea in a wearable dialysis device: a reappraisal of electro-oxidation, Artif. Organs 38 (12) (2014) 998–1006.

[90] J.C. Wright, A.S. Michaels, A.J. Appleby, Electrooxidation of urea at the ruthenium titanium-oxide electrode, AIChE J. 32 (9) (1986) 1450–1458.

[91] M. Ikematsu, K. Kaneda, M. Iseki, H. Matsuura, M. Yasuda, Electrolytic treatment of human urine to remove nitrogen and phosphorus, Chem. Lett. 35 (6) (2006) 576–577.

[92] B.A. Till, L.J. Weathers, P.J.J. Alvarez, Fe(0)-supported autotrophic denitrification, Environ. Sci. Technol. 32 (5) (1998) 634–639.

[93] M.A. Tipple, N. Shusterman, L.A. Bland, M.A. McCarthy, M.S. Favero, M.J. Arduino, M.H. Reid, W.R. Jarvis, Illness in hemodialysis patients after exposure to chloramine contaminated dialysate, ASAIO Trans. 37 (4) (1991) 588–591.

[94] B. Peck, B. Workeneh, H. Kadikoy, S.J. Patel, A. Abdellatif, Spectrum of sodium hypochlorite toxicity in man-also a concern for nephrologists, NDT Plus 4 (4) (2011) 231–235.

[95] J.F. Patzer, S.K. Wolfson, S.J. Yao, Reactor control and reaction-kinetics for electrochemical urea oxidation, Chem. Eng. Sci. 45 (8) (1990) 2777–2784.

[96] S.J. Yao, S.K. Wolfson, M.A. Krupper, K.J. Wu, Controlled-potential controlled-current electrolysis: in vitro and in vivo electrolysis of urea, Bioelectrochem. Bioenerg. 13 (1–3) (1984) 15–24.

[97] B. Schuenemann, E. Quellhorst, H. Kaiser, G. Richter, K. Mundt, E. Weidlich, G. Loeffler, M. Zachariae, O. Schunk, Regeneration of filtrate and dialysis fluid by electro-oxidation and absorption, Trans. Am. Soc. Artif. Intern. Organs 28 (1) (1982) 49–53.

[98] R.W. Keller, S.J. Yao, J.M. Brown, S.K. Wolfson, M.V. Zeller, Electrochemical removal of urea from physiological buffer as the basis for a regenerative dialysis system, Bioelectrochem. Bioenerg. 7 (3) (1980) 469–485.

[99] S.J. Yao, S.K. Wolfson, J.M. Tokarsky, B.K. Ahn, De-ureation by electrochemical oxidation, Bioelectrochem. Bioenerg. 1 (1–2) (1974) 180–186.

[100] M. Fels, Recycle of dialysate from the artificial kidney by electrochemical degradation of waste metabolites: continuous reactor investigations, Med. Biol. Eng. Comput. 20 (3) (1982) 257–263.

[101] M. Tuncer, M. Sarikaya, T. Sezer, S. Ozcan, G. Suleymanlar, G. Yakupoglu, F.F. Ersoy, Chemical peritonitis associated with high dialysate acetaldehyde concentrations, Nephrol. Dial. Transplant. 15 (12) (2000) 2037–2040.

[102] V. Schwenger, C. Morath, A. Salava, K. Amann, Y. Seregin, R. Deppisch, E. Ritz, A. Bierhaus, P.P. Nawroth, M. Zeier, Damage to the peritoneal membrane by glucose degradation products is mediated by the receptor for advanced glycation end-products, J. Am. Soc. Nephrol. 17 (1) (2006) 199–207.

[103] L.M.S.C. Inc, Electrolytic Pretreatment of Urine, National Aeronautics & Space Administration, 1977.

[104] A. Kraft, Doped diamond: a compact review on a new, versatile electrode material, Int. J. Electrochem. Sci. 2 (5) (2007) 355–385.

[105] M.C. Hernández, N. Russo, M. Panizza, P. Spinelli, D. Fino, Electrochemical oxidation of urea in aqueous solutions using a boron-doped thin-film diamond electrode, Diam. Relat. Mater. 44 (2014) 109–116.

[106] E. Urbanczyk, M. Sowa, W. Simka, Urea removal from aqueous solutions-a review, J. Appl. Electrochem. 46 (10) (2016) 1011–1029.

[107] M. Fels, Recycle of dialysate from the artificial kidney by electrochemical degradation of waste metabolites: small-scale laboratory investigations, Med. Biol. Eng. Comput. 16 (1) (1978) 25–30.

[108] K. Koster, H. Wendt, J. Gallus, G. Krisam, H.D. Lehmann, Regeneration of hemofiltrate by anodic-oxidation of urea, Artif, Organs 7 (2) (1983) 163–168.

[109] V.M. Grinval'd, G.M. Leshchinskii, V.V. Rodin, S.I. Strelkov, A.A. Iakovleva, Unit of electrochemical oxidation of hemodialysis products–development and research, Med. Tekh. (2) (2003) 3–7.

[110] W. Simka, J. Piotrowski, G. Nawrat, Influence of anode material on electrochemical decomposition of urea, Electrochim. Acta 52 (2007) 5696–5703.

[111] W. Simka, J. Piotrowski, A. Robak, G. Nawrat, Electrochemical treatment of aqueous solutions containing urea, J. Appl. Electrochem. 39 (7) (2009) 1137–1143.

[112] V. Amstutz, A. Katsaounis, A. Kapalka, C. Comninellis, K.M. Udert, Effects of carbonate on the electrolytic removal of ammonia and urea from urine with thermally prepared IrO2 electrodes, J. Appl. Electrochem. 42 (9) (2012) 787–795.

[113] K. Cho, M.R. Hoffmann, Urea degradation by electrochemically generated reactive chlorine species: products and reaction pathways, Environ. Sci. Technol. 48 (19) (2014) 11504–11511.

[114] H. Li, Q. Yu, B. Yang, Z. Li, L. Lei, Electro-catalytic oxidation of artificial human urine by using BDD and IrO2 electrodes, J. Electroanal. Chem. 738 (2015) 14–19.

[115] N. Bazaev, Investigation of carbon materials for urea degradation via electrolysis for systems with dialysis regeneration unit, Nephrol. Dial. Transplant. 33 (suppl_1) (2018) i511.

[116] J.F. Patzer, S.J. Yao, S.K. Wolfson, R. Ruppelkerr, Urea oxidation-kinetics via cyclic voltammetry - application to regenerative hemodialysis, Bioelectrochem. Bioenerg. 22 (3) (1989) 341–353.

[117] A.E. Bolzan, T. Iwasita, Determination of the volatile products during urea oxidation on platinum by on line mass spectroscopy, Electrochim. Acta 33 (1988) 109–112.

[118] J.R. Rumble, CRC Handbook of Chemistry and Physics, 99th Edition, CRC Press/ Taylor & Francis, Boca Raton, FL, 2018 (Internet Version 2018.

[119] E. Nouri-Nigjeh, H.P. Permentier, R. Bischoff, A.P. Bruins, Electrochemical oxidation by square-wave potential pulses in the imitation of oxidative drug metabolism, Anal. Chem. 83 (14) (2011) 5519–5525.

[120] E. Nouri-Nigjeh, R. Bischoff, A.P. Bruins, H.P. Permentier, Electrochemical oxidation by square-wave potential pulses in the imitation of phenacetin to acetaminophen biotransformation, Analyst 136 (23) (2011) 5064–5067.

[121] [ONLINE], Retrieved from: https://www.rug.nl/research/portal/files/42215355/Complete_thesis.pdf.

[122] Y.C. Cheng, C.C. Fu, Y.S. Hsiao, C.C. Chien, R.S. Juang, Clearance of low molecular-weight uremic toxins p-cresol, creatinine, and urea from simulated serum by adsorption, J. Mol. Liq. 252 (2018) 203–210.

[123] T. Kameda, S. Ito, T. Yoshioka, Kinetic and equilibrium studies of urea adsorption onto activated carbon: adsorption mechanism, J. Dispersion Sci. Technol. 38 (7) (2017) 1063–1066.

[124] M.J. Weston, P.G. Langley, M.H. Rubin, M.A. Hanid, P. Mellon, R. Williams, Platelet function in fulminant hepatic failure and effect of charcoal haemoperfusion, Gut 18 (11) (1977) 897–902.

[125] X. Yang, S. Xin, Y. Zhang, T. Li, Early hemoperfusion for emergency treatment of carbamazepine poisoning, Am. J. Emerg. Med. 36 (6) (2018) 926–930.

[126] M. Touam, F. Martinez, B. Lacour, R. Bourdon, J. Zingraff, S. Di Giulio, T. Drueke, Aluminum-induced, reversible microcytic anemia in chronic renal failure: clinical and experimental studies, Clin. Nephrol. 19 (6) (1983) 295–298.

[127] C.Y. Yin, M.K. Aroua, W.M.A.W. Daud, Review of modifications of activated carbon for enhancing contaminant uptakes from aqueous solutions, Separ. Purif. Technol. 52 (3) (2007) 403–415.

[128] G. Eknoyan, G.J. Beck, A.K. Cheung, J.T. Daugirdas, T. Greene, J.W. Kusek, M. Allon, J. Bailey, J.A. Delmez, T.A. Depner, J.T. Dwyer, A.S. Levey, N.W. Levin, E. Milford, D.B. Ornt, M.V. Rocco, G. Schulman, S.J. Schwab, B.P. Teehan, R. Toto, G. Hemodialysis Study, Effect of dialysis dose and membrane flux in maintenance hemodialysis, N. Engl. J. Med. 347 (25) (2002) 2010–2019.

[129] A. Gil, F.C.C. Assis, S. Albeniz, S.A. Korili, Removal of dyes from wastewaters by adsorption on pillared clays, Chem. Eng. J. 168 (3) (2011) 1032–1040.

[130] J.H. Kim, J.C. Kim, J.H. Moon, J.Y. Park, K.K. Lee, E. Kang, H.C. Kim, B.G. Min, C. Ronco, Development of a cold dialysate regeneration system for home hemodialysis, Blood Purif. 28 (2) (2009) 84–92.

[131] C. Giordano, R. Esposito, P. Bello, E. Quarto, F.M. Gonzalez, Cold carbon apparatus for hemodialysis, J. Dial. 1 (2) (1976) 165–179.

[132] C. Giordano, R. Esposito, P. Bello, A cold charcoal depurator for the adsorption of high quantities of urea, Kidney Int. Suppl. (7) (1976) S284-S288.

[133] D. Deepak, Evaluation of adsorbents for the removal of metabolic wastes from blood, Med. Biol. Eng. Comput. 19 (6) (1981) 701–706.

[134] V. Wernert, O. Schaf, H. Ghobarkar, R. Denoyel, Adsorption properties of zeolites for artificial kidney applications, Microporous Mesoporous Mater. 83 (1–3) (2005) 101–113.

[135] C.H. Ooi, W.K. Cheah, Y.L. Sim, S.Y. Pung, F.Y. Yeoh, Conversion and characterization of activated carbon fiber derived from palm empty fruit bunch waste and its kinetic study on urea adsorption, J. Environ. Manag. 197 (2017) 199–205.

[136] H.D. Lehmann, R. Marten, I. Fahrner, C.A. Gullberg, Urea elimination using a cold activated-carbon artificial tubulus for hemofiltration, Artif. Organs 5 (4) (1981) 351–356.

[137] Y. Fujita, S. Okazaki, Adsorptive activity of activated carbon for urea in aqueous-solutions, Nippon Kagaku Kaishi (4) (1990) 352–356 1990.

[138] M.S. Tijink, M. Wester, G. Glorieux, K.G. Gerritsen, J. Sun, P.C. Swart, Z. Borneman, M. Wessling, R. Vanholder, J.A. Joles, D. Stamatialis, Mixed matrix hollow fiber membranes for removal of protein-bound toxins from human plasma, Biomaterials 34 (32) (2013) 7819–7828.

[139] W.K. Cheah, Y.L. Sim, F.Y. Yeoh, Amine-functionalized mesoporous silica for urea adsorption, Mater. Chem. Phys. 175 (2016) 151–157.

[140] F. Meng, M. Seredych, C. Chen, V. Gura, S. Mikhalovsky, S. Sandeman, G. Ingavle, T. Ozulumba, L. Miao, B. Anasori, Y. Gogotsi, MXene sorbents for removal of urea from dialysate: a step toward the wearable artificial kidney, ACS Nano 12 (10) (2018) 10518–10528.

[141] R.W. Coughlin, Effect of surface groups on adsorption of pollutants, NSCEP (1970) 17020.

[142] V. Chaudhary, S. Sharma, An overview of ordered mesoporous material SBA-15: synthesis, functionalization and application in oxidation reactions, J. Porous Mater. 24 (3) (2017) 741–749.

[143] T. Ukmar, O. Planinsek, Ordered mesoporous silicates as matrices for controlled release of drugs, Acta Pharm. 60 (4) (2010) 373–385.

[144] M. Kruk, M. Jaroniec, C.H. Ko, R. Ryoo, Characterization of the porous structure of

SBA-15, Chem. Mater. 12 (7) (2000) 1961–1968.

[145] R. Huirache-Acuna, R. Nava, C.L. Peza-Ledesma, J. Lara-Romero, G. Alonso-Nuez, B. Pawelec, E.M. Rivera-Munoz, SBA-15 mesoporous silica as catalytic support for hydrodesulfurization catalysts-Review, Materials 6 (9) (2013) 4139–4167.

[146] O. Cheung, N. Hedin, Zeolites and related sorbents with narrow pores for CO2 separation from flue gas, RSC Adv. 4 (28) (2014) 14480–14494.

[147] W.K. Cheah, K. Ishikawa, R. Othman, F.Y. Yeoh, Nanoporous biomaterials for uremic toxin adsorption in artificial kidney systems: a review, J. Biomed. Mater. Res. B Appl. Biomater. 105 (5) (2017) 1232–1240.

[148] M.N.V.R. Kumar, R.A.A. Muzzarelli, C. Muzzarelli, H. Sashiwa, A.J. Domb, Chitosan chemistry and pharmaceutical perspectives, Chem. Rev. 104 (12) (2004) 6017–6084.

[149] M. Rinaudo, Chitin and chitosan: properties and applications, Prog. Polym. Sci. 31 (7) (2006) 603–632.

[150] C.K.S. Pillai, W. Paul, C.P. Sharma, Chitin and chitosan polymers: chemistry, solubility and fiber formation, Prog. Polym. Sci. 34 (7) (2009) 641–678.

[151] J. Benesch, P. Tengvall, Blood protein adsorption onto chitosan, Biomaterials 23 (12) (2002) 2561–2568.

[152] K.R. Pandit, I.A. Nanayakkara, W. Cao, S.R. Raghavan, I.M. White, Capture and direct amplification of DNA on chitosan microparticles in a single PCR-optimal solution, Anal. Chem. 87 (21) (2015) 11022–11029.

[153] H. Parra-Barraza, M.G. Burboa, M. Sanchez-Vazquez, J. Juarez, F.M. Goycoolea, M.A. Valdez, Chitosan-cholesterol and chitosan-stearic acid interactions at the air-water interface, Biomacromolecules 6 (5) (2005) 2416–2426.

[154] R. Riva, H. Ragelle, A. des Rieux, N. Duhem, C. Jérôme, V. Préat, Chitosan and chitosan derivatives in drug delivery and tissue engineering, in: R. Jayakumar, M. Prabaharan, R.A.A. Muzzarelli (Eds.), Chitosan for Biomaterials II, Springer Berlin Heidelberg, Berlin, Heidelberg, 2011, pp. 19–44.

[155] M. Amidi, E. Mastrobattista, W. Jiskoot, W.E. Hennink, Chitosan-based delivery systems for protein therapeutics and antigens, Adv. Drug Deliv. Rev. 62 (1) (2010) 59–82.

[156] S. Jing, T. Yamaguchi, Selective chemisorption of urea by chitosan coated dialdehyde cellulose, Nippon Kagaku Kaishi (1) (1990) 104–108 1990.

[157] X. Chen, W.J. Li, W. Zhong, T.Y. Yu, Investigation of adsorption properties of chitosan/Cu(II) compex in chitosan-silk fibroin blend membranes as adsorbents for urea, Chin. J. Biomed. Eng. 16 (3) (1997) 284–288.

[158] J. Liu, X. Chen, Z. Shao, P. Zhou, Preparation and characterization of chitosan/Cu (II) affinity membrane for urea adsorption, J. Appl. Polym. Sci. 90 (4) (2003) 1108–1112.

[159] Y.G. Zhou, Y.D. Yang, X.M. Guo, G.R. Chen, Effect of molecular weight and degree of deacetylation of chitosan on urea adsorption properties of copper chitosan, J. Appl. Polym. Sci. 89 (6) (2003) 1520–1523.

[160] A. Pathak, S.K. Bajpai, Preparation of Cu(II)-Immobilized chitosan (CIC) and preliminary urea uptake study, Polym. Plast. Technol. 47 (9) (2008) 925–930.

[161] A. Pathak, S.K. Bajpai, Chitosan-magnetite nanocomposites for effective removal of urea in "magnetic hemodialysis therapy": a novel concept, J. Appl. Polym. Sci. 114 (5) (2009) 3106–3109.

[162] L.D. Wilson, C. Xue, Macromolecular sorbent materials for urea capture, J. Appl. Polym. Sci. 128 (1) (2013) 667–675.

[163] C. Xue, L.D. Wilson, Kinetic study on urea uptake with chitosan based sorbent materials, Carbohydr. Polym. 135 (2016) 180–186.

[164] X. Liu, S.J. Sun, Y.H. Tang, S.S. Li, J.H. Chang, L.A. Guo, Y.D. Zhao, Preparation and kinetic modeling of cross-linked chitosan microspheres immobilized Zn(II) for urea adsorption, Anal. Lett. 45 (12) (2012) 1632–1644.

[165] Y.G. Zhou, Sorption of Urea by the Complex of Chitosan-Cu(II), J. Hebei Univ. (Nat Sci Ed.) 19 (2) (1999) 140–143.

[166] A. Pathak, S.K. Bajpai, Cu(II)-cross-linked chitosan membrane (CCCM): preparation, characterization and urea removal study using the diffusion-cell model (DCM), Des, Monomers Polym. 12 (1) (2009) 43–55.

[167] R.B. Penland, S. Mizushima, C. Curran, J.V. Quagliano, Infrared absorption spectra of inorganic coördination complexes. X. Studies of some metal-urea complexes, J. Am. Chem. Soc. 79 (7) (1957) 1575–1578.

[168] T. Theophanides, P.D. Harvey, Structural and spectroscopic properties of metal-urea complexes, Coord. Chem. Rev. 76 (1987) 237–264.

[169] T. Uragami, K. Takigawa, Permeation and separation characteristics of ethanol-water mixtures through chitosan derivative membranes by pervaporation and evapomeation, Polymer 31 (4) (1990) 668–672.

[170] X. Chen, Z.Z. Shao, Y.F. Huang, Y. Huang, P. Zhou, T.Y. Yu, Influence of cross-linking agent content on structure and properties of glutaraldehyde crosslinked chitosan membranes, Acta Chim. Sin. 58 (12) (2000) 1654–1659.

[171] Q.F. Zhou, F. Yang, Q.X. Guo, S. Xue, A new organocatalytic process of cyclo-trimerization of acetylenic ketones mediated by 2,4-pentanedione, Synlett (2) (2007) 215–218 2007.

[172] E. Verheyen, J.P. Schillemans, M. van Wijk, M.A. Demeniex, W.E. Hennink, C.F. van Nostrum, Challenges for the effective molecular imprinting of proteins, Biomaterials 32 (11) (2011) 3008–3020.

[173] C. Alexander, H.S. Andersson, L.I. Andersson, R.J. Ansell, N. Kirsch, I.A. Nicholls, J. O'Mahony, M.J. Whitcombe, Molecular imprinting science and technology: a survey of the literature for the years up to and including 2003, J. Mol. Recognit. 19

(2) (2006) 106–180.

[174] L. Chen, X. Wang, W. Lu, X. Wu, J. Li, Molecular imprinting: perspectives and applications, Chem. Soc. Rev. 45 (8) (2016) 2137–2211.

[175] K. Haupt, Imprinted polymers—tailor-made mimics of antibodies and receptors, Chem. Comm. (2) (2003) 171–178.

[176] T. Takeuchi, J. Haginaka, Separation and sensing based on molecular recognition using molecularly imprinted polymers, J. Chromatogr. B Biomed. Sci. Appl. 728 (1) (1999) 1–20.

[177] E.L. Holthoff, F.V. Bright, Molecularly imprinted xerogels as platforms for sensing, Accounts Chem. Res. 40 (9) (2007) 756–767.

[178] C. Alvarez-Lorenzo, A. Concheiro, Molecularly imprinted polymers for drug delivery, J. Chromatogr. B 804 (1) (2004) 231–245.

[179] G. Wulff, J. Liu, Design of biomimetic catalysts by molecular imprinting in synthetic polymers: the Role of transition state stabilization, Accounts Chem. Res. 45 (2) (2012) 239–247.

[180] Y. Cheng, K.L. Xu, H. Li, Y.F. Li, B. Liang, Preparation of urea-imprinted cross-linked chitosan and its adsorption behavior, Anal. Lett. 47 (6) (2014) 1063–1078.

[181] T. Alizadeh, A. Akbari, A capacitive biosensor for ultra-trace level urea determination based on nano-sized urea-imprinted polymer receptors coated on graphite electrode surface, Biosens. Bioelectron. 43 (1) (2013) 321–327.

[182] H.T. Lian, B. Liu, Y.P. Chen, X.Y. Sun, A urea electrochemical sensor based on molecularly imprinted chitosan film doping with CdS quantum dots, Anal. Biochem. 426 (1) (2012) 40–46.

[183] Y.P. Chen, B. Liu, H.T. Lian, X.Y. Sun, Preparation and application of urea electrochemical sensor based on chitosan molecularly imprinted films, Electroanalysis 23 (6) (2011) 1454–1461.

[184] M.H. Lee, J.L. Thomas, M.H. Ho, C. Yuan, H.Y. Lin, Synthesis of magnetic molecularly imprinted poly(ethylene-co-vinyl alcohol) nanoparticles and their uses in the extraction and sensing of target molecules in urine, ACS Appl. Mater. Interfaces 2 (6) (2010) 1729–1736.

[185] B. Khadro, C. Sanglar, A. Bonhomme, A. Errachid, N. Jaffrezic-Renault, Molecularly imprinted polymers (MIP) based electrochemical sensor for detection of urea and creatinine, Procedia Eng. 5 (2010) 371–374.

[186] T. Alizadeh, Preparation of molecularly imprinted polymer containing selective cavities for urea molecule and its application for urea extraction, Anal. Chim. Acta 669 (1–2) (2010) 94–101.

[187] T. Alizadeh, M. Akhoundian, Z. Movahed, Indirectly determination of urea using chloride ion selective electrode after its extraction and preconcentration by molecularly imprinted polymer, Anal. Bioanal. Electrochem. 1 (4) (2009) 246–256.

[188] C.Y. Huang, T.C. Tsai, J.L. Thomas, M.H. Lee, B.D. Liu, H.Y. Lin, Urinalysis with molecularly imprinted poly(ethylene-co-vinyl alcohol) potentiostat sensors, Biosens. Bioelectron. 24 (8) (2009) 2611–2617.

[189] E. Grillon, R. Gallo, M. Pierrot, J. Boileau, E. Wimmer, Isolation and X-ray structure of the intermediate dihydroxyimidazolidine(Dhi) in the synthesis of glycoluril from glyoxal and urea, Tetrahedron Lett. 29 (9) (1988) 1015–1016.

[190] R. Shapiro, N. Chatterjie, Cyclization reactions of ninhydrin with aromatic amines and ureas, J. Org. Chem. 35 (2) (1970) 447–450.

[191] T. Shimizu, S. Fujishige, A newly prepared surface-treated oxystarch for removal of urea, J. Biomed. Mater. Res. 17 (4) (1983) 597–612.

[192] M.N.Z. Abidin, P.S. Goh, A.F. Ismail, N. Said, M.H.D. Othman, H. Hasbullah, M.S. Abdullah, B.C. Ng, S. Kadir, F. Kamal, Highly adsorptive oxidized starch nanoparticles for efficient urea removal, Carbohydr. Polym. 201 (2018) 257–263.

[193] H. Bing-Lin, X.B. Zhao, Study of the oxidation of crosslinked β-cyclodextrin polymer and its use in the removal of urea. I, React. Polym. 18 (3) (1992) 229–235.

[194] M.S. Eisen, Urea sorbent, U.S. Patent 8,220,643 B2 (2014).

[195] R.J. Wong, Materials for Removal of Toxins in Sorbent Dialysis and Methods and Systems Using Same A1 WO2013101888, 2014.

[196] E. Kuntz, J.P. Quentin, Process for extracting urea from a solution with alkenyl-laromatic polymers with α-ketoalhydic groups, U.S. Patent 4,012,317 (1977).

[197] J.P. Quentin, E. Kuntz, Alkenylaromatic polymers with α-ketoalhydic groups, U.S. Patent 3,933,753 (1976).

[198] M.J. Poss, H. Blom, A. Odufu, R. Smakman, Macromolecular ketoaldehydes, U.S. Patent 6,861,473 B2, 2005.

[199] R. Smakman, A.W. van Doorn, Urea removal by means of direct binding, Clin. Nephrol. 26 (Suppl 1) (1986) S58–S62.

[200] R. Smakman, Macromolecular carbonyl groups containing material suitable for use as sorbent for nitrogen compounds. U.S. Patent 4,897,200, 1990.

[201] I.J. Stern, R.S. Izzo, Z.W. Jo Wang, W.E. Beschorner, Mechanism of urea nitrogen binding by proposed oxidized starch gastrointestinal absorbents, Experientia 31 (9) (1975) 1065–1066.

[202] J.A.W. Jong, R. Smakman, M.E. Moret, M.C. Verhaar, W.E. Hennink, K.G.F. Gerritsen, C.F. Van Nostrum, Reactivity of (vicinal) carbonyl compounds with urea, ACS Omega 7 (4) (2019) 11928–11937.

[203] A.W. van Doorn, Regeneration of dialysate, Artif. Organs 3 (2) (1979) 190–192.

[204] J.A.W. Jong, M.E. Moret, M.C. Verhaar, W.E. Hennink, K.G.F. Gerritsen, C.F. van Nostrum, Effect of substituents on the reactivity of ninhydrin with urea, ChemistrySelect 3 (4) (2018) 1224–1229.