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Chemical Engineering Research and Design

journal homepage: www.elsevier.com/locate/cherd

Electrochemical separation of organic acids and proteins for food and biomanufacturing

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ARTICLE INFO

Article history:
Received 10 August 2021
Received in revised form 12 November 2021
Accepted 4 December 2021
Available online 10 December 2021

Keywords:
Electrochemical separation
Electrodialysis
Electrosorption
Protein recovery
Organic acid recovery

ABSTRACT

Over the past decades, the rapid population growth coupled with increased awareness towards nutrition has driven the demand for organic acids (e.g., carboxylates) and proteins, through pharmaceutical and food products. Close to 50–70% of the overall production cost of organic acids and proteins comes from separation processes during manufacturing. Recently, electrochemically-mediated separations have gained significant attention as a sustainable solution for lowering chemical consumption and achieving process intensification. Here, we review progress in electrochemical processes for the recovery of organic acids and proteins, in food and biomanufacturing contexts. We highlight aspects of the electrochemical engineering of these systems, selection of electrode materials, and discuss the underlying separation mechanisms. We emphasize the need for understanding molecular level selectivity coupled with engineering design, for broadening the applicability of electrochemical platforms for selective bioproduct purification. On the long term, we envision electrochemical separations as a sustainable and competitive process for the recovery of value-added molecules in food and biomanufacturing.

1. Introduction

1.1. *Worldwide food and biomanufacturing*

Global demand for food and biomanufacturing has risen due to the rapidly growing population. In particular, food demand is predicted to increase by 60% from 2019 to 2050 (Ladha-Sabur et al., 2019). Resource and energy-intensive food manufacturing contributes to carbon emissions, and presents a challenge for achieving the 2 °C limit in global temperature increase set by the Paris Agreement (Clark et al., 2020; Tilman et al., 2011). Processes with increased efficiency and lower carbon footprint, combined with reducing food loss and food waste, are essential to a sustainable food supply (Mirabella et al., 2014). Additionally, innovations in biomanufacturing are key to meeting the widespread demand for therapeutic and nutrient products. These products range from primary metabolites (e.g., ethanol, amino acids), secondary metabolites (e.g., penicillin), to proteins and enzymes (Zhang et al., 2017b). Up to date, in food and biomanufacturing, 50–70% of the production cost comes from the separation processes for product recovery (e.g., purification of organic acids) (Handojo et al., 2019). Thus, the development of environmentally benign and energy-efficient separations is essential to meet sustainability goals, as well as to satisfy global the demand for bioproducts (Gottschalk et al., 2012).

Electrochemical separation processes have a potential to innovate traditional downstream processing methods through the integration of renewable energy sources and the reduction or even complete elimination of chemical input. While electrochemical separations have been extensively explored for the removal of inorganic ions, there are growing applications in the separation of organic molecules, proteins, and cells (Fritz et al., 2021). Therefore, this review highlights key areas of development for electrochemical separations in food and biomanufacturing, major opportunities and challenges for industrial applications, and emerging research directions. We review the growing interest in electrosorption-based processes, the developmnet of selective electrodes, and membrane-based electrochemical systems. Throughout, we discuss the selection of electrode materials, the design of electrochemical systems, and the underlying separation mechanisms.

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https://doi.org/10.1016/j.cherd.2021.12.009

1.2. *Types of common organic acids and proteins in food and biomanufacturing processes*

The fast-growing food and biomanufacturing have been closely related to the increasing consumption of organic acids and proteins. The demand for organic acids and proteins has seen an annual growth rate between 5 and 9.5%, respectively (Campisi, 2021; Leuchtenberger et al., 2005; Taylor et al., 2015).

Organic acids are widely used as precursors for synthesizing chemical derivatives in numerous fields such as food, pharmaceutical, and chemical industries (Hábová et al., 2004; Kang and Chang, 2005; Zaman et al., 2017). For instance, succinic acid is an indispensable chemical for the production of biodegradable polymers, detergents, food seasonings, and even anticarcinogenic agents (Berglund et al., 1991; Huh et al., 2006; Kang and Chang, 2005). Oxalic acid is a reducing organic acid, widely used as metal treatment, dye, and bleaching agents as shown in Table 1 (Riemenschneider and Tanifuji, 2000). Lactic acid has experienced the most significant market growth due to its versatile use from textiles, cosmetics, and food to medical sutures and drug release systems (Fig. 1(a) and Table 1) (Kim and Moon, 2001; Lipinsky and Sinclair, 1986; Taylor et al., 2015; Yang et al., 2007; Zacharof and Lovitt, 2013; Zaman et al., 2017). In general, the market price of organic acids tends to drop as the manufacturing size expands, as shown in Fig. 1(a). However, the inverse relationship between the market price and market size is not applicable to acrylic acid, which serves as a raw material for numerous chemical syntheses. In this respect, acrylic acid production is considered a major driving factor for the market growth of acrylate esters, resulting in a $2500/ton global market price for acrylic acid in 2013 (Taylor et al., 2015).

Until the early 2000s, industrial production of amino acids has grown mainly to meet the demand for glutamate, which is used as a flavor enhancer and an additive for animal feed (Table 1) (Ikeda, 2003; Leuchtenberger et al., 2005). Today, growing interest in health accelerates the increase of the market size and value of amino acids for pharmaceutical and nutraceutical products. Many studies have shown that intake of amino acids not only improves muscular and tissues performance, but also benefits neurotransmitter and hormone transport (Andlauer and Fürst, 2002; Kraemer et al., 2006; Maughan et al., 2007). To meet the high demand in the market, most of 300 types of amino acids are synthesized in vitro. The synthetic amino acids and amino acid derivatives are widely used in clinical chemistry, pharmaceuticals, and neurochemistry as important pharmaceutical intermediates (Ikeda, 2003; Poinsot et al., 2014).

Proteins play an important role in many areas such as cell metabolism, growth, and the immune system of living organisms. Thus, applications of proteins have extended from food manufacturing to medicinal uses and health supplements (Guo et al., 2007) (Table 2). Most therapeutic proteins and food proteins are extracted from natural sources. Some therapeutic proteins such as Etanercept and Bevacizumab are engineered to be compatible with human beings. For example, Etanercept is a dimeric protein synthesized from two naturally occurring human 75-kDa TNF receptors (Smola et al., 1991). Bevacizumab is originally derived from a mouse antibody, with the originally human-incompatible chains replaced with with human-compatible substituents (Scott, 2007). More recently, unmodified proteins such as monoclonal antibodies have been recognized as therapeutics. Pharmaceutical companies have explored them for clinical purposes, and consequently, nearly 100 genuine unmodified therapeutic proteins have been approved by the European Union (EU) and the USA (Dimitrov, 2012). Fig. 1(b) shows the market size and price of protein-based products. In particular, the prices of therapeutic proteins far exceed those of food proteins, mainly due to their extremely low availability and extensive purification processes (Creamer et al., 2014).

2. Separation technologies for the purification of organic acids and proteins

2.1. *Current separation processes and their limitations*

There is an urgent need for innovation in separations, to meet the growing demand for organic acid and biomolecule production (Campisi, 2021; Leuchtenberger et al., 2005; Saraswat et al., 2013; Taylor et al., 2015). Currently, over 350 protein-based medicines are being evaluated in late-stage clinical trials by pharmaceutical companies (Saraswat et al., 2013). Downstream processes of fractionation and high-level purification account for over 50% of the total manufacturing cost with a large amount of waste stream, and devising sustainable and efficient separation methods is a key challenge across multiple scales (Handojo et al., 2019; Saraswat et al., 2013). Table 3 shows common separation techniques widely used in the food and bio-industry for the purification of products such as organic acids, proteins, and peptides. For simplicity, the classification of separation techniques was based on the "Separation Process Principles" textbook (Seader et al., 1998).

2.1.1. *Precipitation and crystallization*

Precipitation and crystallization are widely used purification methods in food and biomanufacturing. They utilize chemical or resolving agents to create a solid phase, by reducing the solubility of the target product (Komesu et al., 2017; Seader et al., 1998). The product is obtained in the form of a finely divided solid, while impurities remain in the feed phase. Precipitation methods are relatively safe and low-cost because they require simple equipment and can be operated at room temperature (Berglund et al., 1991; Guo et al., 2007). For instance, during the fermentation processes, carboxylic acids are precipitated in the form of calcium carboxylate with excess calcium carbonate or calcium hydroxide (Handojo et al., 2019; Kumar et al., 2010; Nakano et al., 2012). Also, leveraging the isoelectric properties and heating, precipitation can form a more compact structure of the target product with a high yield rate and a high protein coagulation rate (Horigome et al., 1990). Although reagents for precipitation and crystallization techniques can be recycled, the recycling process requires additional chemicals and extreme conditions such as low pH and high temperature. Consequently, these methods are often limited by the large volume of wastewater is produced, associated with the high energy consumption and equipment corrosion (Handojo et al., 2019; Komesu et al., 2017).

2.1.2. *Liquid–liquid extraction*

Extraction methods take advantage of the differential solubilities of target molecules between two phases. Liquid–liquid extraction relies on a fluid phase that is immiscible with the feed solvent to selectively extract one or more solutes of interest (Komesu et al., 2017; Seader et al., 1998). The method can be used for bioproduct and organic acid separation from fermentation broths. Common organic solvents are butyl alcohol (oxygen-bearing hydrocarbons), tributyl phosphate (phosphorus-bonded oxygen-bearing solvents), and dodecyl amine (high molecular weight aliphatic amines). These solvents are known to meet important criteria such

Table 1 – Examples of commercially available organic acids (carboxylates and amino acids), their natural sources, and major applications.

Type of organic acid	Name	Natural sources	Major applications	Reference
Carboxylic acids	Acetic acid	Vinegar, fruits	Synthesis of rubber, plastics, acetate fibers; vinegar	Huang et al. (2007), López-Garzón and Straathof (2014), Zaman et al. (2017)
	Butyric acid	Milk, vegetable oil	Textiles, biofuel, food, pharmaceuticals	Du et al. (2012), Karimi and Vahabzadeh (2014), Zaman et al. (2017)
	Citric acid	Citrus fruits	Food preservation, beverage flavoring, cleaning, polishing agent	Huang et al. (2007), López-Garzón and Straathof (2014), Pazouki and Panda (1998)
	Gulonic acid	Wine, fruits, honey, rice	Food additives, Vitamin C precursor, chelating agent	Huang et al. (2007), López-Garzón and Straathof (2014), Vandenberghe et al. (2018)
	Lactic acid	Fermented vegetables	Cosmetic, pharmaceutical, textiles	Panoff (2020), Zaman et al. (2017)
	Oxalic acid	Fruits, cocoa, nuts, seeds	Dye, bleaching agents, chemical synthesis	Riemenschneider and Tanifuji (2000)
	Succinic acid	Broccoli, meat, cheese	Beverage flavoring, seasoning, chemical synthesis	Featherstone (2015), Huh et al. (2006), Kang and Chang (2005), Zaman et al. (2017)
Amino acids	Aspartic acid Glutamine Histidine Tryptophan Lysine	Oysters, meats, avocado Beef, spinach, parsley Soy protein, eggs, peanuts Celery, onions, lentils, carrots Eggs, whitefish, smelts	Biosynthesis of proteins, animal feed, flavor enhancer, pharmaceuticals, nutraceutical industries	Andlauer and Fürst (2002), Górska-Warsewicz et al. (2018), Leuchtenberger et al. (2005), Nag (2017)

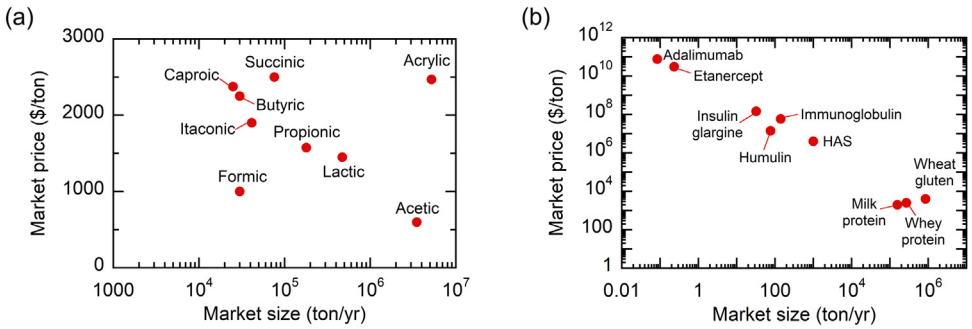

Fig. 1 – Estimated market price ($/ton) with respect to the market size (ton/yr): (a) organic acids (Taylor et al., 2015; Zacharof and Lovitt, 2013) and (b) proteins ((Dimitrov, 2012) and (GoodPx, 2021) for the annual sales and prices of Adalimumab, Humulin, Etanercept, and Insulin glargine. Farrugia and Scaramuccia (2017) for immunoglobulin. Berman (2021) and Chen et al. (2013) for the market size and price of human serum albumin (HAS). Day (2011) and Day et al. (2006) for the market size and price of wheat gluten. Lagrange et al. (2015) and Clal.it (2021a, b) for the market sizes and prices for milk and whey protein.

as distribution coefficient, separation capacity, and selectivity (Handojo et al., 2019; Hong and Hong, 2005; Komesu et al., 2017; Pazouki and Panda, 1998). Aqueous two-phase system (ATPS) is often applied to separate biomolecules such as proteins, viral particles, and plasmid DNA due to the stabilizing effect of phase-building polymers (Saraswat et al., 2013). Despite long-term development, liquid–liquid extraction still has critical limitations for industrial applications. For instance, low distribution coefficients for organic acids and high toxicity of the extractants to microorganisms impede application for in-situ extractive fermentation (Gao et al., 2009; Kurzrock and Weuster-Botz, 2010). A large exchange area between two phases is inevitable for the high production capacity, making the equipment large and expensive. Furthermore, sequential solvent recovery processes (e.g., extractive distillation) are still required, following the liquid–liquid extraction process (Seader et al., 1998).

2.1.3. *Filtration*

Filtration exploits a membrane as a barrier, through which solutes selectively pass based on their permeabilities and concentration gradient (Seader et al., 1998). For microporous membranes, the diffusion rate of molecules through the pores determines the selectivity. On the other hand, for nonporous membranes, both solubility and diffusion drive the separation process. During dialysis, small and soluble molecules are transported through a porous membrane with a high diffusion rate. Microfiltration can permeate molecules with size between 0.02 and 10 μm, while nanofiltration permeates smaller molecules between 1 and 20 nm (Fig. 2) (Seader et al., 1998).

Pressure-driven filtration techniques provide unique advantages of continuous operation and high selectivity. For instance, nanofiltration selectively recovers organic acids from mineral ions and residual carbohydrates based

Table 2 – Examples of commercially available food and therapeutic proteins, their natural sources or manufacturing companies, and major applications.

Type of main use	Protein	Source or manufacturing company	Major applications	Reference
Food proteins	Wheat gluten	Plant (e.g., wheat)	Flour fortification, meats, pet food	Day et al. (2006)
	Collagen	Meat, fish, egg	Cosmetic, membrane, sealant	Avila Rodríguez et al. (2018)
	Milk protein (concentrates)	Milk	Nutrition products, sports powders, processed cheese	Lagrange et al. (2015)
	Whey protein (concentrates)	Whey	Sports beverages, nutritional supplements	Lagrange et al. (2015)
	Human serum albumin	Human plasma	Medical use (e.g., replacement of lost fluid)	Chen et al. (2013)
	Immunoglobulin	Plasma cells	immunoassays, diagnosis, disease treatment	Farrugia and Scaramuccia (2017)
Therapeutic proteins	Etanercept	Amgen Wyeth	Immune diseases	Dimitrov (2012)
	Bevacizumab	Genentech Roche Chugai	Cancer	
	Adalimumab	Abbott Eisai	Immune diseases	
	Insulin glargine	Sanofi-Aventis	Diabetes	
	Interferon beta-1a	Biogen Idec	Multiple sclerosis	
	Insulin (Humulin)	Eli Lilly	Diabetes	

on sieving size, solution–diffusion, and Donnan exclusion (Fig. 2). The filtration technique is also widely used for peptide fractionation from protein hydrolysates (Brans et al., 2004). Ultrafiltration showed high efficiency in the recovery of proteins such as leaf proteins (Fig. 2). During ultrafiltration, the leaf protein particles remained in the feed, while other solute molecules cross over the membrane (Koschuh et al., 2004). Despite their advantages, filtration methods have intrinsic problems of membrane fouling and clogging, followed by high energy consumption and subsequent maintenance/replacement cost (Dlask and Václavíková, 2018). Thus, many filtration techniques, especially the forward osmosis, have beeen studied for up-concentration of organic acids as pre- or post-treatment steps, coupled with other separation methods such as centrifugation and crystallization (Garcia-Aguirre et al., 2020; Law and Mohammad, 2018; Law et al., 2019).

2.1.4. *Liquid chromatography*

Liquid chromatography enables the separation of molecules based on their affinity on the stationary solid particles in a packed bed. The stationary phase of a chromatography column consists of a micro- or nano-porous structure with a high surface area. Thus, feed components move through the column at different rates depending on the binding affinity towards the stationary phase (Seader et al., 1998). Over the past decades, a variety of chromatography for different application purposes has been developed (Table 3). Ion exchange chromatography can separate anions and cations, while affinity or size-exclusion chromatography is used to capture and purify recombinant proteins and peptides (Rodriguez et al., 2020; Saraswat et al., 2013). Finely designed stationary phases allow producing highly purified products. Hence, the traditional separation of biomolecules has relied heavily on the column chromatography technique (Saraswat et al., 2013). For example, the manufacturing of antibodies (immunoglobulins) on an industrial scale has used protein-A chromatography, a type of affinity chromatography, over 20 years (Liu et al., 2010). However, obtaining highly purified peptide fractions often requires a series of columns that are highly expensive and time-consuming; as a result, the complicated column arrangement often leads to low productivity (He et al., 2016). In addition, a short lifetime of the column stationary phase makes it challenging to scale up for the manufacturing of biomolecules (Saraswat et al., 2013).

2.2. *Electrochemical separation technologies*

Electrochemical technologies have received significant attention for separations due to their versatile, energy-efficient, and environmentally benign operation. Ionic species migrate via electrically induced fields, and can be separated based on their charge, size, electric mobility, and solvation (Kim et al., 2021a; Sirés and Brillas, 2012; Srimuk et al., 2020; Su, 2020b; Yoon et al., 2019). As described in Section 2.1, current technologies such as precipitation, crystallization, filtration, and solvent extraction require high energy consumption, a large volume of chemicals, and complex waste disposal. On the other hand, electrochemical approaches consume relatively low energy and do not require chemical additives for the regeneration processes, thus providing greater sustainability (Handojo et al., 2019; Huang et al., 2007). Especially, the electrochemical separation systems can be advantageous for the demineralization of brackish water (TDS < 5000 ppm) (Al-Karaghouli and Kazmerski, 2013; Walha et al., 2007). In this concentration range, electrodialysis is known to be the most energy-efficient system (0.7–2.5 kW h/m^3) among various desalination technologies, including multistage flash distillation (19.58–27.25 kW h/m^3), vapor compression (16.26 kW h/m^3), and reverse osmosis (RO, 1.5–2.5 kW h/m^3) (Al-Karaghouli and Kazmerski, 2013). Furthermore, electrochemical systems offer a natural integration with renewable energy sources such as solar and wind (Al-Karaghouli and Kazmerski, 2013; Srimuk et al., 2020). Still, a more comprehensive techno-economic analysis (TEA) is required to validate the cost benefits and feasibility of integrating electrochemical technologies with sustainable energy. The continued development of functional materials can promote molecularly selective electrosorption for minority ions (Kim et al., 2020a; Su and Hatton, 2017b; Su et al., 2017b). Finally, the advancement of electrochemical systems engineering is expected to enable a broad range of industrial applications (Handojo et al., 2019; Tang et al., 2019).

Table 3 – Current separation processes in food and biomanufacturing: short descriptions, their advantages and disadvantages, and examples of applications (Dlask and Václavíková, 2018; Handojo et al., 2019; Komesu et al., 2017; Saraswat et al., 2013; Seader et al., 1998; Zhang et al., 2017a).

Technique	Separation by	Example of technique	Advantage	Disadvantage	Example of application
Precipitation and crystallization	Phase creation or addition	Neutralization Acidification Isoelectric precipitation Organic solvent precipitation Salting out	Simple operation; Low technological barriers and risks due to existing infrastructure	Large consumption of chemicals resulting in the waste stream; Reagent recovery process resulting in high energy consumption; Low product purity	Lactic acid (Nakano et al., 2012) Alfafa leaf protein (Zhang et al., 2017a)
Liquid–liquid extraction	Phase addition	Liquid–liquid extraction Aqueous two-phase extraction	Simple operation; Low risk in operational condition without extreme temperature	Unfavorable distribution coefficient and toxicity of conventional agents; The large size of equipment for a high exchange area; Solvent recovery process; Low product purity	Picolinic acid (Waghmare et al., 2011) Bovine serum albumin (Waziri et al., 2004)
Filtration	Barrier with pressure or concentration gradient	Microfiltration Ultrafiltration Nanofiltration Membrane distillation Forward osmosis Dialysis	Easy scalability; Continuous operation; Facile integration with other methods; Applicable in various product size	Membrane fouling; High cost of membranes; Polarization problem; Low product purity	Acetic acid (Ecker et al., 2012) Whey protein (Kumar et al., 2013)
Chromatography	Solid agent	Affinity chromatography Ion exchange chromatography Size-exclusion chromatography Counter current-simulated moving bed chromatography	Long-term continuity Easy quantitative analysis; High product purity; Unnecessary pre- or post-treatment;	High cost of columns; Difficult scalability; Low productivity; Chemical and mechanical instability of columns	Immunoglobulins (Liu et al., 2010)

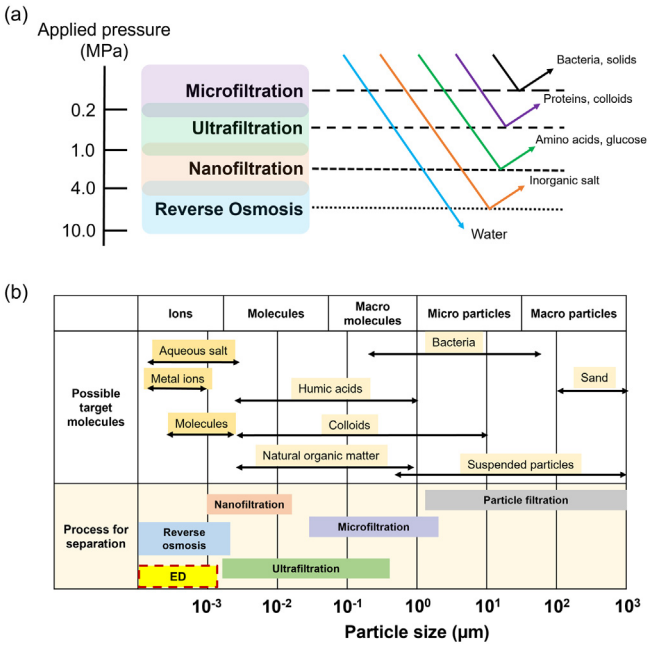

Fig. 2 – (a) Classification of membranes, retention characters, and approximation of the applied pressures and (b) Overview of membrane-based separation techniques and their cut-off range depending on the size of target molecules. Panel (a) is adapted from Zhang et al. (2017a) and (b) from Warsinger et al. (2018).

2.2.1. *Electrosorption*

The interfacial chemistry of electrodes and membranes serves as a key component for driving separations. Thus, numerous studies have explored various electrode materials such as functionalized carbons (Ji et al., 2018; Leong and Yang, 2020; Oyarzun et al., 2018; Trunzer et al., 2021), intercalating materials (Boota and Gogotsi, 2019; Srimuk et al., 2020), and redox-active polymers (Chen et al., 2020a; Su and Hatton, 2017a) (Fig. 3). Most commonly, porous carbon electrodes such as activated carbon, graphene, and functionalized carbon are used in electrosorption (often referred as capacitive deionization) (Kang et al., 2020; Srimuk et al., 2020; Suss et al., 2015; Yoon et al., 2019). Faradaic materials have also been widely explored for electrosorption. Based on material types and conversion mechanisms, the faradaic materials can be classified into intercalating/conversion materials such as Prussian blue analogues (Lee et al., 2017) and Ag/AgCl (Srimuk et al., 2019) and redox-active polymers, including metallopolymers (e.g., PVF (Kim et al., 2020b), PFMAm (Vapnik et al., 2021), and polyaniline (Cui et al., 2011)) and radical organic-polymer (e.g., PTMA (Medina et al., 2021)). In general, electrosorption involves distinct steps of adsorption and desorption. During adsorption, the ionic species travel to the electrode surface (within the electrical double layer), and are removed from the solution phase. Then, the electrodes are regenerated by releasing the captured ionic species during the desorption process, often by applying opposite polarity or removing the charge (Yoon et al., 2019). Capacitive deionization, has been explored for the desalination and the separation of inorganic ions (i.g., Na^+ and Cl^-) (Oren, 2008; Porada et al., 2013), alkali and alkali earth metals (i.g., Li^+ and Mg^{2+}) (Lee et al., 2013), and alkali metals (i.g., Na^+ and K^+) (Lee et al., 2017). Recently, electrosorption has been expanded to selective recovery/removal of heavy metals, micropollutants, and even organic species (Chen et al., 2020a; Kim et al., 2020a, b; Su et al., 2016). In this review, we discuss electrosorption for the selective separation of organic species of relevance to food and biomanufacturing, especially organic acids and proteins.

2.2.2. *Electrochemical membrane system*

Various electrochemical membrane systems have been introduced for separation processes as summarized in Fig. 3. Most commonly, an electrochemical membrane system uses ion exchange membranes to modulate selectivity based on the charge and molecular sizes. The ion exchange membrane is made up of polymeric supports with charged groups on the surface layer. Cation exchange membranes often contain sulfonic, phosphonic, or carboxylic acid as charged groups, while tertiary amine is often used as a functional group within anion exchange membranes (Vogel and Meier-Haack, 2014). Beyond the functional groups, the nature of the polymeric supports and pore sizes (membrane cut-off) play important roles in determining membrane selectivity and separation performance (Güler et al., 2013). Thus, membrane selectivity is often modulated by selection of the charged groups, and tuning

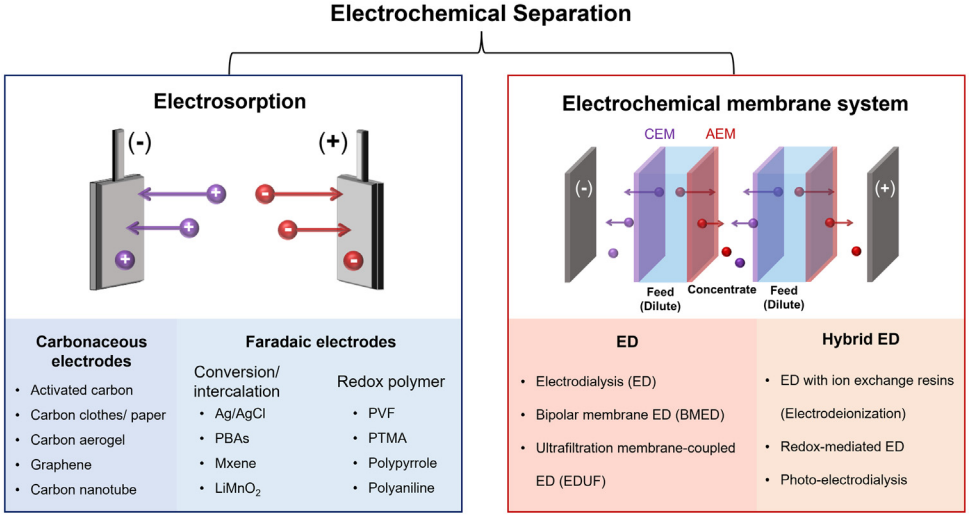

Fig. 3 – Overview of electrochemical separation technologies, mainly classified into electrosorption and electrochemical membrane systems. Electrosorption is categorized by material types and adsorption mechanisms. The electrochemical membrane system is categorized into an ED system with various membrane types and a hybrid ED system.

Table 4 – Examples of the electrochemically mediated system in the recovery of organic acids and proteins: Target organic acids or proteins, electrochemical system, solution and operation condition, recovery, and energy consumption. (ED: electrodialysis, BMED: bipolar membrane electrodialysis. BP: bipolar, AEM: anion exchange membranes, CEM: cation exchange membrane, CC: constant current mode, CV: constant voltage mode, Wk: working electrode, Ctr: counter electrode).

Organic acids/proteins	Electrochemical system	Feed solution and (Operation condition)	Recovery	Energy consumption	Ref. (Section)
Crotonic acid	Electrosorption (Activated carbon)	5 mM crotonic acid (CV: 1.2 V, 60 min)	0.1 mmol/$g_{electrode}$	—	Hack et al. (2019) (Section 3.1.1)
Succinic acid	BMED (BP-AEM-CEM-BP)	0.5 M Na_2Suc (CC: 12.5 mA/cm^2, 250 min)	0.35 mol/L	2.3 kW h/kg_{acid}	Fu et al. (2014) (Section 3.1.2)
Whey proteins	ED	8200 mg/L sweet whey with ash and 20% solid content (CC: 13.5 mA/cm^2, CV: 0.85 V per stack)	90% desalted	17.7 kJ/L_{whey}	Greiter et al. (2002) (Section 3.2.1)
β-lactoglobulin (β-LG)	Bipolar membrane electroacidification (BMEA)	5% whey protein isolate, 2 g/L KCl, 20 g/L Na_2SO_4 (CC 2 A until 60 V then hold CV 60 V)	44.0% β-LG with 98% purity	—	Bazinet et al. (2004) (Section 3.2.1)
β-lactoglobulin (β-LG)	Redox-mediated ED	7 ppm β-LG, 100 mM NaCl (CV: 1.0 V, 4.6 h)	98% β-LG, 99% salt removal	2.6 kW h/m^3	Kim et al. (2021b) (Section 3.2.1)
Morpholine (Mp)	BMED (BP-AEM-BP)	0.15 M MpH_2SO_4 0.3 M Na_2SO_4 (CC: 30 mA/cm^2, 150 min)	62.7% Mp	4.27 kW h/kg_{Mp}	Jiang et al. (2013) (Section 3.3.1)
Phenylglycine (Phg)	Closed-loop circulation BMED (BP-CEM-BP)	0.3 M Na_2SO_4 100 mL of 2 M NaPhg in a separate batch (CC: 20 mA/cm^2, 60 min)	94.1% Phg	0.69 kWh/kg_{Phg}	Zhou et al. (2016) (Section 3.3.2)
Ibuprofen (Ibu)	ED (CEM-AEM-CEM)	0.50 mM Ibu 7.93 mM NH_4HCO_2 (CV: 60 V, 6 h)	57% Ibu	—	José et al. (2021) (Section 3.3.3)
α-chymotrypsin (α-CHY)	Electrosorption (PVF/CNT (wk), CNT (ctr))	5 mg α-CHY with 50 mM carbonate (0.4 V vs Ag/AgCl, 60 s)	~ 480 mg/g_{PVF}	—	Su et al. (2017a) (Section 3.4.3)
Bovine serum albumin (BSA)	Electrosorption (PVF/CNT (wk), CNT (ctr))	5 mg BSA with 50 mM phosphate (0.4 V vs Ag/AgCl, 60 s)	~ 250 mg/g_{PVF}	—	Su et al. (2017a) (Section 3.4.3)

the pore sizes which controls the membrane cut-off (Handojo et al., 2019).

In the electrochemical membrane systems, the choice of membranes and their arrangements depends on the target molecules (Fig. 3) (Klaysom et al., 2010; Lee et al., 2008; Li et al., 2019). Electrodialysis is one of the most widely used electrochemical membrane systems, first proposed in 1890 to purify sugar syrup (Amiri and Karimi, 2018; Bazinet, 2005; Shaposhnik and Kesore, 1997). Maigrot and Sebates introduced a three-compartment electrochemical cell divided by two permanganate papers, which served as semi-permeable membranes (Montiel et al., 2014). As the potential was applied to the carbon electrodes, the ionic species, mainly cations such as Na^+, K^+, Ca^{2+}, and Mg^{2+}, were removed from the sugar syrup (Shaposhnik and Kesore, 1997). Then in 1900, the system was named 'electrodialysis' by Schollmeyer and patented mainly for the purification of sugar syrup. The current features of ED systems have been developed in the 1930s, with the introduction of ion exchange membranes and with the alternative arrangement of cation and anions exchange membranes (Shaposhnik and Kesore, 1997; White, 2015). In recent years, ED has been implemented in a wide range of fields such as pharmaceutical, food, chemical, and downstream processes (Huang et al., 2007; Konarev, 2015; Wang et al., 2019). Compared to the traditional filtration systems (e.g., reverse osmosis), the ED system has been recognized as a green technology due to low energy consumption and absence of chemical additives in the process (Handojo et al., 2019; Zaman et al., 2017). The ED system consists of a stack of cation and anion exchange membranes (Fig. 3). This alternative arrangement of membranes allows for the separation of ionic species from feed water (Al-Amshawee et al., 2020; Handojo et al., 2019; Shaposhnik and Kesore, 1997). For instance, when the electrical energy is applied, positive ions migrate through the cation exchange membrane, while negative ions migrate in opposite direction through the anion exchange membrane, demineralizing water (Al-Amshawee et al., 2020). Up to date, the ED system has been demonstrated with various combinations of membranes such as ion exchange membranes (Kim and Moon, 2001), bipolar membranes (BMED) (Tongwen, 2002), and ultrafiltration membranes (EDUF) (Dlask and Václavíková, 2018). More recently, the ED system has been hybridized with ion exchange resins (Greiter et al., 2002), redox materials (Kim et al., 2019, 2021b), and photoanode (Kim et al., 2018; Mohandass et al., 2021).

3. Electrochemically mediated separations in food and biomanufacturing

Electrochemically mediated separations are widely demonstrated in various organic acids and protein separations. Table 4 provides an overview of some highlighted examples of various electrochemically mediated separations in food and biomanufacturing. As shown in Table 4, numerous electrochemically mediated systems, ranging from ED systems to redox functionalized electrodes, have been introduced either to separate ions from target biomolecules or to capture valuable molecules reversibly.

3.1. *Application of electrochemically mediated separation in fermentation processes*

With an increased interest in renewable resources, fermentation processes have been applied to organic acids productions from biomass. During fermentation, biomass is broken down and reassembled into desired products by microorganisms under anaerobic conditions (Zacharof and Lovitt, 2013). The availability of biomass is extensive not only in crops and woods but also in waste streams such as agricultural wastes, sludge, and wastewater. In this regard, the amount of biomass is estimated to be 170 billion tons per year (Schlosser and Blahušiak, 2011; Song and Lee, 2006; Zaman et al., 2017). Thus, the conversion of biomass to organic acids via fermentation is environmentally benign and effectively reduces the carbon footprint compared to the conventional chemical production process using petroleum. Due to the sustainable, fast, and selective production of organic acids, the global market for fermentation products has been rising at an average annual growth rate of 4.7% since the early 2000s (Soccol et al., 2008). In particular, over 60% of lactic acid is produced through the fermentation process (Hábová et al., 2004).

3.1.1. *Organic acids purification*

Recent studies have explored electrodialysis as an alternative technique for the purification of organic acids in the fermentation process. ED does not require additional chemicals or high energy consumption during operation. Besides, it enables the recovery and acidification of carboxylate salts simultaneously (Kim and Moon, 2001), while current separation techniques such as solvent extraction and adsorption involve multiple processes to recover organic acids (López-Garzón and Straathof, 2014). With current technologies, 50–70% of the overall production cost of organic acid via fermentation comes from the recovery processes (Handojo et al., 2019; Huh et al., 2006). Thus, process intensification via ED could enhance the economic feasibility of acid production.

Several studies have demonstrated an outstanding performance of the ED and its derivative systems for the recovery of organic acids such as acetic (Chukwu and Cheryan, 1999; Weier et al., 1992), citric (Sun et al., 2017; Widiasa et al., 2004), lactic (Boontawan et al., 2011; Hábová et al., 2004; Kim and Moon, 2001), succinic (Fu et al., 2014; Szczygiełda et al., 2017), and butyric (Du et al., 2012) acids from fermentation broths. In the late 1990s, many organic acids were up-concentrated by the conventional ED system (Fig. 3). For instance, acetate was successfully up-concentrated from the fermentation broth through multiple-stage ED processes (Chukwu and Cheryan, 1999). With 20 alternative stacks of anion and cation exchange membranes (total effective area of 0.46 m^2), the ED system produced a concentrated acetate stream and concentrated reactant stream. Then two additional ED processes further up-concentrated the acetate from 50 $g_{acetate}$/L to 134 $g_{acetate}$/L, while the concentrated unreacted glucose and other nutrients were recycled back to the fermentation process.

Recently, Gausmann et al. proposed electrochemical pH-shift extraction and crystallization for the recovery of succinic acid (Gausmann et al., 2020) and itaconic acid (Gausmann et al., 2021) from the fermentation broth. In general, the optimized pH of fermentation for carboxylic acids is between 5.5–7; thus, most carboxylic acid products are in anionic species. The work leveraged electrochemical water-splitting reactions to swing the pH for both extraction and crystallization of carboxylates. For instance, in acidic pH, the succinic acid is extracted using a tertiary amine extractant, with the extractant being regenerated through a pH swing. The recovery of succinic acid is further accelerated by a pH-shift crystallization. During the electrolysis, the dissociation equilibrium of the acid was shifted towards protonated form (H_2A)

at the anode side. The protonated carboxylic acids, including succinic acid, are often less soluble than the deprotonated states (HA^- or A^{2-}) (Kocks et al., 2021). Thus, the succinic acid was crystallized as the system reached the solubility limit (Gausmann et al., 2020). The electrochemical pH-shift extraction and crystallization method successfully recovered succinic acid with a crystal size distribution comparable to the commercially available products (Gausmann et al., 2020).

Few studies have been conducted on the enrichment of organic acids via electrosorption. Hack et al. (2019) applied a capacitive deionization system for up-concentrating crotonic acid after fermentation processes. The study showed an effective up-concentration performance (up to a factor of 2) and highlighted the importance of the solution pH on the adsorption of organic acids. For instance, the adsorption capacity of 0.1 $mmol_{crotonate}/g_{electrode}$ was achieved at a feed pH of 7. On the other hand, the adsorption dropped to 0.02 $mmol_{crotonate}/g_{electrode}$ at the feed pH of 5 because of the partial dissociation of the crotonic acid ($pKa_{crotonic\ acid}$: 4.69) (Hack et al., 2019). The drastic decrease in adsorption capacity is due to a deficient amount of dissociated organic species and coion repulsion of undissociated organic acids (Wagner et al., 2021). During the adsorption, the charged electrodes are balanced not only by adsorbing the dissociated organic acids but also by releasing the undissociated organic acids attached to the surface of electrodes (physisorption) (Wagner et al., 2021). Thus, there is a clear need for the judicious design of the electrosorption system and operating conditions for up-concentrating organic acids. Moreover, the electrosorption technique has been integrated with the column chromatography system (Brammen et al., 2017; Knizia et al., 2003). The electrochemically modulated chromatography system using a conducting stationary phase (e.g., conducting resins or polymers) enables the separation of organic species based on the interactions between charged stationary phase and molecules. Unlike the conventional chromatography, electrochemically modulated chromatography can regenerate the stationary phase by applying appropriate potential without any use of eluting agents (Brammen et al., 2017). For instance, Knizia et al. (2003) applied the graphite particles as a stationary phase to separate three carboxylic acids: crotonic, fumaric, and maleic acids. By applying potential gradients or potential drops, electrochemically-modulated chromatography could even separate stereoisomers of maleic (cis-isomer) and fumaric acids (trans-isomer) (Knizia et al., 2003).

3.1.2. *Bipolar membrane ED for simultaneous enrichment and acidification*

To achieve simultaneous up-concentration and acidification of organic acids, most ED systems adopted bipolar membrane (Fu et al., 2014; Hábová et al., 2004; Kim and Moon, 2001; Sun et al., 2017; Szczygiełda et al., 2017). The bipolar membrane is made up of the cation-selective and anion-selective layers. Each side of the layer enables to dissociate of water into H^+ and OH^- with 80% of the charge efficiency, leading to the production of concentrated organic acid in a single process step as shown in Fig. 4(a) (Hanada et al., 1993; Handojo et al., 2019).

In 2001, Kim et al. (Kim and Moon, 2001) demonstrated a single-stage ED process to produce lactic acid and sodium hydroxide by stacking the membranes in the following order from left-to-right: bipolar (BP), anion exchange (AEM), cation exchange (CEM), and bipolar (BP) membranes (Fig. 4(a)). This membrane arrangement allowed three production streams: acid stream (between a cation-exchange layer of the BP and AEM), feed stream (between AEM and CEM), and base stream (between an anion-exchange layer of the BP and CEM). As the lactate crossed the AEM, lactic acid is produced in the acid stream with free hydrogen ions generated on the cation exchange layer of the BP. In the same manner, as sodium ions crossed the CEM, it formed sodium hydroxide with hydroxide ions generated on the anion exchange layer of the BP. As a result, sodium lactate was successfully converted into lactic acid and sodium hydroxide with 96% and 93% conversions, respectively. Moreover, Fu et al. (2014) investigated various membrane stack configurations of bipolar membrane electrodialysis (BMED) for succinic acid recovery in terms of yield, current efficiency, and energy consumption. The result confirmed that the configuration of BP-AEM- CEM-BP showed optimal performance, such as high acid production and current efficiency (90%) and comparable energy consumption (~2.3 kW $h/kg_{succinicacid}$) over BP-AEM-BP or BP-CEM-BP configurations (Fig. 4(c) and (d)).

The ED system can be modified by adding ion exchange resins in the feed channel to enhance the recovery of organic acids as depicted in Fig. 4(b) (Boontawan et al., 2011; Handojo et al., 2019; Widiasa et al., 2004; Yuan et al., 2015). The major bottleneck of the conventional ED system is low ionic conductivity and high solution resistance as the ions migrate from the treating stream to the concentrated stream (Handojo et al., 2019; Widiasa et al., 2004). In the 1950s, Walters et al. (Walters et al., 1955) proposed an electrodeionization system (EDI) to enhance the ionic conductivity in dilute solution by adding ion exchange resins in the feed stream. The ion exchange resins serve as the ionic transport channel by adsorbing the ions, mainly H^+ and OH^-, on the beads and enhancing the ionic conductivity in the dilute stream (Handojo et al., 2019). The continuous water-splitting reaction on the surface of the resins allows regeneration of the resin beads over time (Handojo et al., 2019; Walters et al., 1955; Widiasa et al., 2004). EDI has been introduced to several organic acid recoveries such as tartaric acid (Zhang et al., 2009), citric acid (Widiasa et al., 2004), lactic acid (Boontawan et al., 2011), and butyric acid (Du et al., 2012) in the fermentation process. For instance, Du et al. (2012) demonstrated that the yield of butyric acid in a fermentation process increased from 85% to 92% with ion wafers in the ED system. In addition, EDI was successfully applied to the separation of amino acids such as glutamate and lysine, exhibiting a 50% improvement in the transport of amino acids (Yuan et al., 2015).

3.2. *Application of electrochemically mediated separation in dairy industry processes*

3.2.1. *Whey desalination via ED*

Saline wastewater management is a challenge for the dairy industry and, depending on the local jurisdiction, salty wastewater from dairy is subject to increasingly strict regulatory requirements (Chen et al., 2018). During the production of semi-hard and hard cheese, salt is added to protein-rich cheese curd to reduce water activity within the curd (Chen et al., 2018, 2020b). The excess moisture expelled from the curd during salting and pressing processes, forming salty whey. Salty whey often cannot be discharged directly to the sewer and thus requires further downstream treatment. Recently, the perspective on whey has shifted from being waste to being a stream worth repurposing and valorizing as it contains functional proteins and peptides, lipids, vitamins, minerals, and lactose (Anil et al., 2018; Smithers, 2008). Whey typically

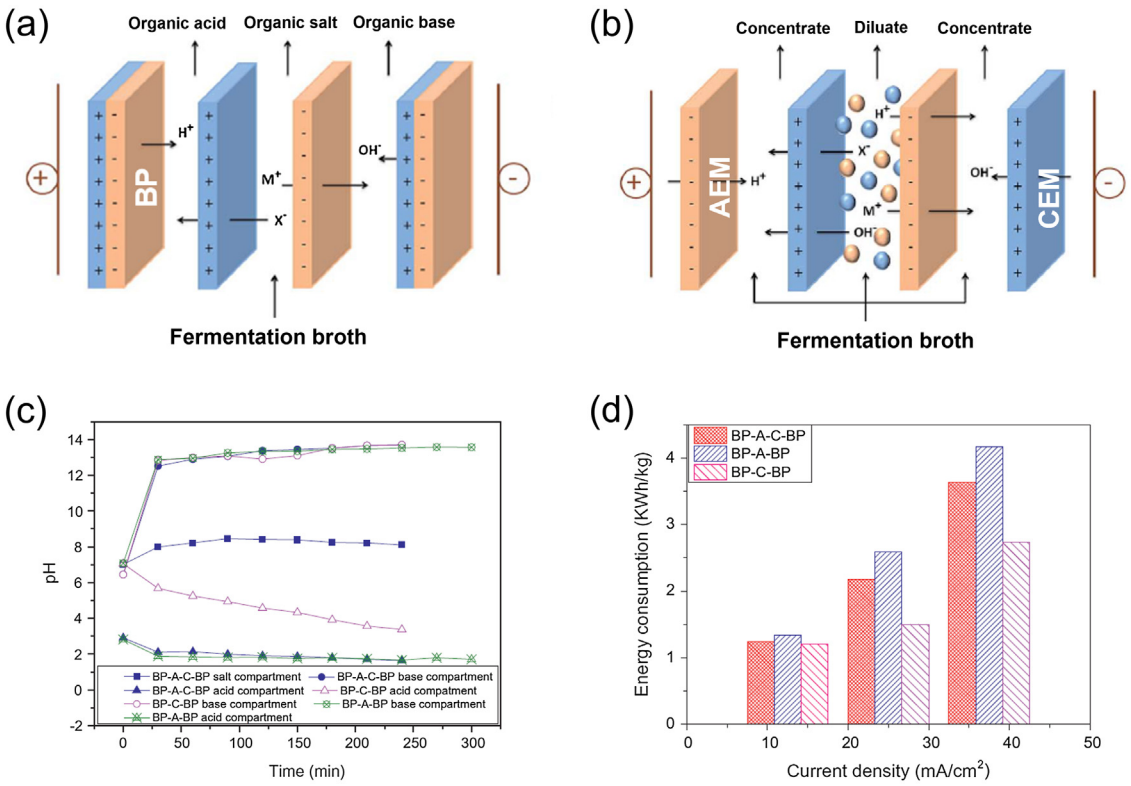

Fig. 4 – Schematics of (a) bipolar membrane electrodialysis (BMED) and (b) electrodialysis with ion exchange resins (electrodeionization, EDI). Performance of succinic acid recovery with the bipolar membrane electrodialysis system: (c) pH and (d) energy consumption. AEM (or A), CEM (or C), and BP represent anion exchange membrane, cation exchange membrane, and bipolar membrane, respectively. Panels (a) and (b) are reproduced from Handojo et al. (2019), and (c) and (d) from Fu et al. (2014).

contains 8–10% minerals on a dry weight basis, and this mineral content can be problematic in whey processing (Gernigon et al., 2011). Additionally, demineralization is necessary to repurpose the whey streams into food products. For example, a 50–70% reduction in mineral content is needed to repurpose whey in ice cream applications, to reduce the salty taste, while a 90–95% reduction in mineral content is needed to repurpose whey in infant formulas (Gernigon et al., 2011).

Between the 1970s and 1980s, numerous studies demonstrated the viability and efficacy of ED to desalinate whey streams (Amundson et al., 1982; Bazinet, 2005; Houldsworth, 1980; Wang et al., 2019). These studies highlighted that (i) ED can demineralize whey up to 90–95%, (ii) a high conductivity was favorable for ED operation since it reduces energy losses, and (iii) the maximum demineralization rate can be obtained at pH close to the whey protein isoelectric point since net neutrally charged proteins are not involved in ion transport.

In 2002, Grieter et al. (Greiter et al., 2002) assessed the energy demand of an ED process versus an ion-exchange process for whey desalination, and determined that ED was favorable in many aspects. While ED could not desalinate the whey to the same degree as ion-exchange (90% and 99% desalination of 8200 mg/L with various ionic species such as Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, and PO_4^{3-}), ED was operated more efficiently. For instance, the cumulative energy demand of ED is significantly lower than that of ion exchange, and the total effluent volume, as well as total salt discharge, is lower for ED as well. Several studies showed that elevated temperatures can further improve the desalination kinetics of ED, perhaps even providing a potential method to utilize low-grade heat for performance enhancement (Law et al., 2013; Merkel et al., 2020).

Recently, ED has been integrated with redox species to lower the energy consumption in the whey protein recovery process (Kim et al., 2021b). A redox-mediated electrodialysis system leverages reversible redox reactions for continuous removal of ionic species in the whey waste streams (Fig. 5(a)). When the redox species are oxidized and reduced, negative and positive ions migrate from treating water to the anodic and cathodic chamber, respectively, and balance the charge neutrality in the electrolyte (Kim et al., 2019, 2020d). Since the standard reduction potential of ferricyanide and ferrocyanide is lower than the water-splitting reaction, the system could reduce the energy consumption by over 51% compared to the conventional ED systems. The system exhibited 99% salt removal (starting from 500 mM NaCl) and valorized >98% of whey contents such as beta-lactoglobulin, alpha-lactalbumin, and lactose in a single operation step (Fig. 5(c) and (d)). Kim et al. also proposed the net-zero waste process by reusing the removed salts in the cheese manufacturing process as illustrated in Fig. 5(b). This net-zero waste process could alleviate the burden of downstream treatment and maintain the electrolyte concentration (Kim et al., 2021b).

3.2.2. *Bipolar membrane ED for pH adjustment and protein fractionation*

As previously mentioned with organic acids, ED with bipolar membranes (BMED) has the potential to combine desalination and pH adjustment steps without any additional chemicals. For example, several studies have used BMED to deacidify the acid whey while simultaneously desalinating it (Dufton et al., 2018; Kravtsov et al., 2020; Merkel et al., 2018).

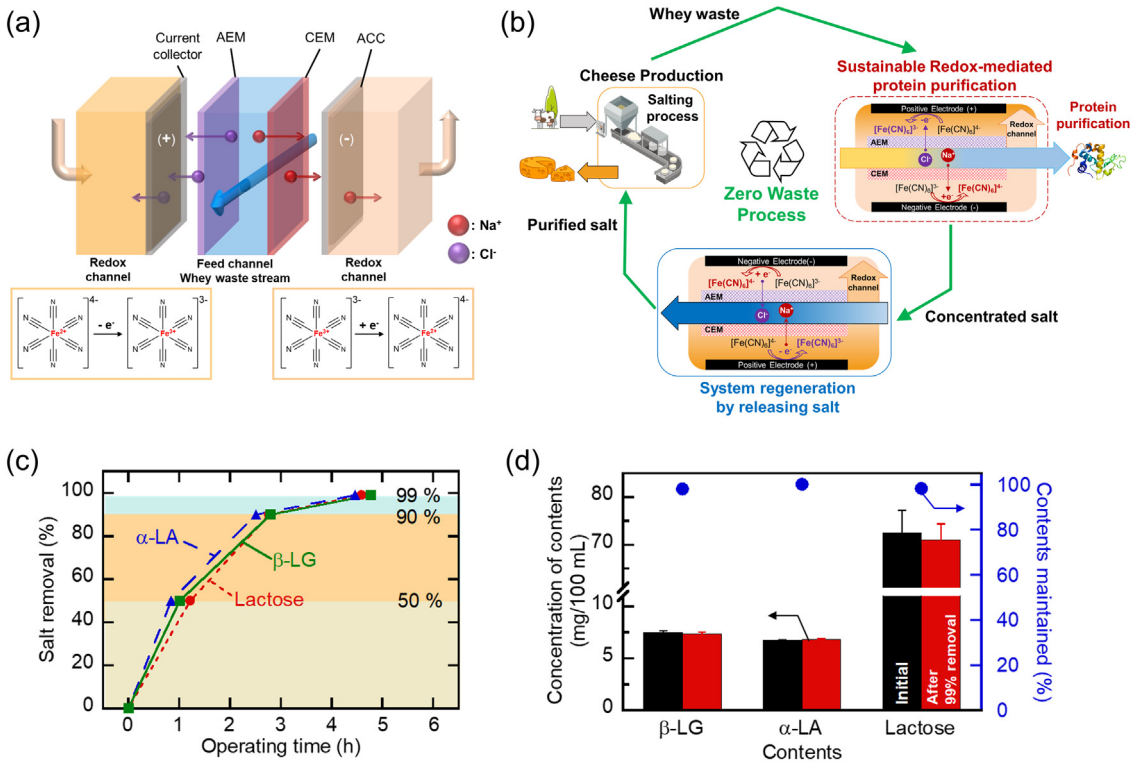

Fig. 5 – Schematics of (a) redox-mediated electrodialysis system and (b) the net-zero waste process; (c) salt removal % and (d) valorization of representative whey contents (beta-lactoglobulin (β-LG), alpha-lactalbumin (α-LA), and lactose) after 99% salt removal. The figure is reproduced from Kim et al. (2021b).

Recently, Chen et al. were able to desalinate whey streams while producing sodium hydroxide and hydrochloric acid with BMED (Chen et al., 2020b). They achieved over 99% demineralization of salty whey and generated high purity acid/base solutions of concentrations of around 3.5 mol/L after the sodium hydroxide pretreatment to remove calcium and magnesium phosphate salts. The base consumed in the pretreatment represented only 9% of the base generated by the BMED process.

BMED also enables the fractionation of whey proteins via pH-controlled precipitations. Despite the unique functional characteristics of individual whey proteins, the lack of consistency in the composition and functionality of whey powders has generated interest in methods that can isolate the individual whey proteins (El-Sayed and Chase, 2011). Bazinet et al. (2004) implemented a bipolar membrane electroacidification (BMEA) system which allowed for the separation of a 98% pure β-lactoglobulin fraction with 44% recovery yield. BMEA has also been used for the precipitation of lipids from whey (Lin Teng Shee et al., 2005, 2007). Lipid separation from whey allows for the effective valorization of the protein fractions. Lin Teng Shee et al. (2005) utilized a BMEA system to acidify cheddar cheese whey from pH 6.3 to 3.7, which increased lipid precipitation by 54% compared to the centrifugation process. Lin Teng Shee et al. (2007) also demonstrated the use of BMEA systems for the delipidation of whey protein concentrate, where the acidification of whey protein concentrate solutions to pH 4.5 doubled the amount of lipid precipitation compared to the centrifugation process. Continued studies in lipid separation via BMED have demonstrated that decreasing ionic strength of whey up to 80% can be favorable for lipid precipitation. Also, higher protein concentration can increase lipid precipitation, but it comes at the cost of some protein precipitating as well (Faucher et al., 2021, 2020).

3.2.3. *Electro-membrane protein and peptide fractionation*

Electrified membrane processes have been widely studied for separating various protein fractions through a combination of size exclusion effects and electric field effects. The traditional methods of membrane filtration and chromatography are often unselective or prohibitively expensive, respectively. Electromembrane filtration combines conventional membrane filtration with electrophoresis to overcome the limitations of traditional methods. For instance, electromembrane filtration up-concentrated α_{s2}-casein f(183–207), a peptide with strong antimicrobial activity, in a solution of casein hydrolysate from 7.5% in the feed to 25% in the permeate (Bargeman et al., 2002). Similar membrane-electrophoretic studies demonstrated the fractionation of α-lactalbumin and β-lactoglobulin (β-LG), the separation of bovine lactoferrin from whey, and the separation of β-LG f(142–148) from β-LG hydrolysates (Galier and Balmann, 2012; Ndiaye et al., 2010; Poulin et al., 2007).

3.2.4. *Electrosorption*

Electrosorption-based separations are relatively few in the dairy industry. Fritz et al. (2020) demonstrated that the incorporation of polyelectrolyte coating onto activated carbon could capture proteins with no applied electric bias (0 V) and subsequently release protein and adsorb salt at 1.2 V (Fig. 6). They found an increase in the amount of protein adsorbed upon electric polarization from 1 to 10 mg/g. They were also able to enrich β-lactoglobulin from whey protein concentrate, demonstrating a level of molecular selectivity of their electrode surfaces. We expect the electrosorption-based separation of dairy proteins and peptides to be an area of growth in the coming years, through the development of tailored electroactive surfaces with a controllable affinity towards target species (Su and Hatton, 2017a).

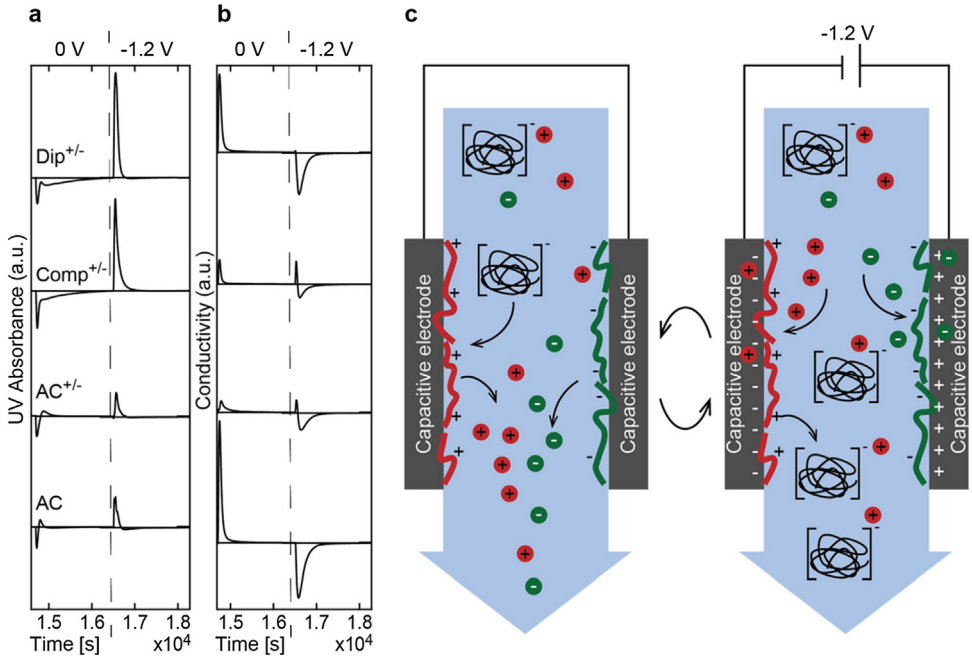

Fig. 6 – Protein and salt separation using an electrical switch. (a) Change in UV signal of the eluent during cycle 5. (b) Change in conductivity of the eluent during cycle 5. (c) Schematic of salt (positive and negative dots) and protein (ravels in square brackets) ad- and desorption. At 0 V proteins adsorb and salt is released (c, left), while at a potential bias, proteins desorb, and salt is stored in the electrodes (c. right). The red and green curved lines at the electrode interface represent the polyelectrolytes. The figure is reproduced from Fritz et al. (2020).

3.3. *Application of electrochemically mediated separation in pharmaceutical processes*

The global pharmaceutical market has experienced a significant growth in the last decades. Over 100 modified therapeutic proteins (e.g., adalimumab and etanercept in Fig. 1(b)) have been approved for clinical use in the European Union and the USA, with sales of over $108 billion. All of the top five biologic drugs in 2010 sales were protein-based, emphasizing the importance of protein synthesis and fractionation (Dimitrov, 2012). Among recent developments of pharmaceutical synthesis and separation technologies, greener and more process-intensified routes such as biocatalytic processes gained interest, to minimize the environmental impact and the production cost (Cue and Zhang, 2009; Huisman and Collier, 2013). Intermediate products from biocatalytic methods are often found in media with salts, impurities, and by-products after their productions. Thus, further processes are essential to purify products (Fehér et al., 2020; Gao et al., 2020; Rottiers et al., 2017). Electrochemical separation technologies such as electrodialysis (ED) have been demonstrated over a wide range of pharmaceutical products for two major processes: (i) modification of the nature of product-containing media by acidification or alkalization and (ii) potential-driven selective migration of ionic or charged bulky products coupled with ion exchange or ultrafiltration membranes (He et al., 2016).

3.3.1. *Pharmaceutical products with amine groups*

Pharmaceutical intermediates often contain functional groups such as amine and carboxyl, so pH adjustment is necessary for their solubility control by ionization or crystallization. As mentioned in Section 3.1, electrochemical methods such as bipolar membrane electrodialysis (BMED) have found their cost-effective and environmentally benign applications in the separation of such intermediate products.

Amine-containing intermediate products, including amino acids, become cations via protonation. They then migrate across a cation exchange membrane and react with OH^- to yield a much more pure product, leaving impurities and by-products in the feed compartment (Gao et al., 2020; Jiang et al., 2013, 2017; Lv et al., 2021). For instance, Jiang et al. (2013) investigated a variety of BMED stack configurations to demonstrate its feasibility of producing morpholine from its sulfate salt. Morpholine can be a building block for the antibiotic linezolid and the anticancer agent gefitinib. Among the three cell configurations (BP-AEM-CEM-BP, BP-CEM-BP, and BP-AEM-BP), the BP-AEM-BP configuration obtained the highest yield of 62.7%, the lowest process cost of 1.20 $/kg, and energy consumption of 4.27 kW h/kg. The exceptional performance of the BP-AEM-BP configuration is mainly due to the direct reaction between OH^- and protonated morpholine. On the other hand, the BP-AEM-CEM-BP configuration showed the highest current efficiency of 83.62%, but also a higher energy consumption due to greater resistance from membranes.

BMED has drawn recent attention as a green alternative for the post-treatment method after chiral resolution. Among chiral resolution techniques, diasteromerization is one of the most widely used methods in the pharmaceutical industry owing to its simple operation and low cost of chemicals (Siedlecka, 2013). For the conversion of the two diastereomeric salts back to their enantiomeric form, excessive addition of the chemical reagents such as NaOH is commonly used. The excessive chemical use not only results in significant alkali waste, but also reduces the yield due to the non-orientation of the chiral flip (Gao et al., 2020). Lv et al. (2021) used BMED as a post-treatment of chiral resolution of S-2-amino-1-butanol ($C_4H_{11}NO$) which is a key intermediate product for ethambutol hydrochloride and one of the most effective antituberculosis

drugs. Under the optimized conditions, the BP-CEM-BP configuration achieved 1.04 mol/L and 92.28% of the conversion rate, making the cost of 2.22 $/kg and energy consumption of 1.88 kW h/kg.

3.3.2. *Pharmaceutical products with carboxylic groups*

In the opposite manner of alkalization process to produce amine-containing products, some amino acids and organic acids are protonated, and purified by electrochemical processes with high yield and low energy consumption (Szczygiełda and Prochaska, 2017; Wang et al., 2020; Zhou et al., 2016). The electrochemical methods such as BMED enabled simultaneous acidification without the use of highly acidic aqueous media or organic solvents (Fehér et al., 2020; Rottiers et al., 2017). Certain organic acids have a problem of low solubilities in aqueous media, which can be overcome by adding polar organic solvents such as primary alcohols (Rottiers et al., 2017). For instance, salicylic acid production using BMED has been extensively studied to find optimal solvent mixture and conditions (Alvarez et al., 1997; Huang et al., 2007; Liu et al., 2015; Rottiers et al., 2017). Rottiers et al. (2017) improved the BMED system by placing two cation exchange membranes at both sides of the solvent mixture. This modification improved the sodium removal towards 99.7% under a high salicylate concentration and a low co-solvent of 1-propanol.

Production of derivatized amino acids via chemical or biochemical synthesis contain organic impurities such as precursors and salts; therefore, multiple separation processes are necessary for complete purification (Fehér et al., 2020; Zhou et al., 2016). Recently, BMED was applied to produce amino acids including glycine derivative amino acids and phenylglycine (Wang et al., 2020; Zhou et al., 2016). Zhou et al. (2016) proposed an in-situ and closed-loop circulation BMED to overcome the poor solubility of phenylglycine in water. Phenylglycine sodium salt was synthesized from the NaOH stream. Then hydrogen, which was generated by the BP, was fed into the phenylglycine sodium salt to produce phenylglycine. Once the pH reached the isoelectric point of the phenylglycine, the product is purified by the filtration process. This intriguing process-intensified electrochemical process showed a yield of 94.1% and energy consumption of 0.69 kW h/kg for phenylglycine. Besides amino acids, recent studies also have proven the feasibility of BMED for the separation of low molecular organic acids such as alpha-ketoglutaric acid, known as a metabolite, and phenylacetic acid, an intermediate for penicillin-G and diclofenac (Fehér et al., 2020; Szczygiełda and Prochaska, 2017).

3.3.3. *Peptides and other pharmaceutical molecules*

Besides pH modulation, electrochemical methods such as ED are also capable of using differential electromigration of charged species for the separation of pharmaceutical intermediates such as peptides from impurities, and even other competing biomolecules (Dlask and Václavíková, 2018; Strathmann, 2010; Suwal et al., 2014).

Peptides, enzymatically hydrolyzed from animal and plant sources, are known for their beneficial attributes such as antimicrobial, anticancer, antithrombotic, and immunomodulatory functions (Korhonen and Pihlanto, 2006). Most bioactive peptides are contained as fragments of complex peptides and proteins with different physicochemical properties. Thus, subsequent fractionation and purification processes are required to separate desired peptides (Laurent and Loubna, 2013). The ultrafiltration membrane-coupled ED system (EDUF) was first introduced to prevent AEM fouling during whey demineralization in 1975. Since then, different configurations and parameters of EDUF have been studied for peptide and protein separation (Doyen et al., 2012; Firdaous et al., 2010; He et al., 2016; Pihlanto-Leppälä, 2000; Poulin et al., 2008; Roblet et al., 2016, 2014; Suwal et al., 2014; Vanhoute et al., 2010). The recent applications of EDUF for peptide separation was reviewed by Dlask and Václavíková (2018). In particular, He et al. (2016) reported that protein hydrolysate obtained from alcalde digestion of rapeseed protein was successfully fractionated using an EDUF containing four ultrafiltration membranes. The operation at 20 V for 6 h yielded three peptide fractions: the anionic fraction with 43.57% of negatively charged amino acids, the cationic fraction with 28.35% of positively charged amino acids, and final rapeseed protein hydrolysate (fraction remaining in the feed channel) (He et al., 2016).

Also, the applicability of electrochemical systems for the purification of pharmaceutical-related molecules, including ibuprofen (José et al., 2021), taurine (Konarev, 2015), and collagen (Chen et al., 2019), have been recently explored. José et al. investigated the ED application to the separation of the ibuprofen from ethyl esters after the enzymatic esterification of *rac*-ibuprofen with ethanol (José et al., 2021). Their ED system with the CEM-AEM-CEM configuration allowed the selective migration of S-enriched anionic ibuprofen without its decomposition, obtaining up to 57% extraction of ibuprofen from impurities and by-products in ethanol media at 60 V for 6 h.

3.4. *Valorization of organic molecules in downstream processes*

3.4.1. *Recovery of organic acids in advanced oxidation processes*

In industrial wastewater treatment, it is unavoidable to generate a wide range of hydrocarbon molecules as byproducts. In particular, the degradation of pollutants by advanced oxidation processes generates a series of hydrocarbon molecules, including organic acids such as acetic and oxalic acids (Parizot et al., 2019; Ruiz et al., 2011), many which can be targeted as products for resource recovery. For example, the degradation of dye wastewater such as indigo and acid yellow 36 resulted in the production of acetate and oxalate (Qu et al., 2015; Ruiz et al., 2011; Yu et al., 2021). Recently, Yu et al. (2021) proposed efficient recovery of organic acids in waste streams using flow-electrode capacitive deionization (FCDI) to lower energy consumption and maintain long-term stability. As shown in Fig. 7(a), FCDI deploys suspended carbon materials as flowing electrodes, to simultaneously capture target species and regenerate the electrodes at the electrolyte reservoirs without additional regeneration treatment (Jeon et al., 2013; Tang et al., 2019). The study showed comparable acetate recovery between conventional ED (71–99%) and FCDI (68–95%) (Fig. 7(b)). Besides, compared to the conventional ED model, FCDI exhibited the enhanced average oxalate recovery rate and the percent recovery up to 0.45 μmol/cm^2 min and 80.1%, respectively (Fig. 7(b) and (c)). The conventional ED system was operated at higher cell voltages between 3.2 to 5.5 V, at current densities ranging from 2.85 to 11.40 A/m^2 (Fig. 7(d)), which could cause the degradation of oxalate at the surface of electrodes. On the other hand, FCDI maintained its cell voltage lower than the conventional ED system throughout the investigated current densities. In particular, below 5.7 A/m^2,

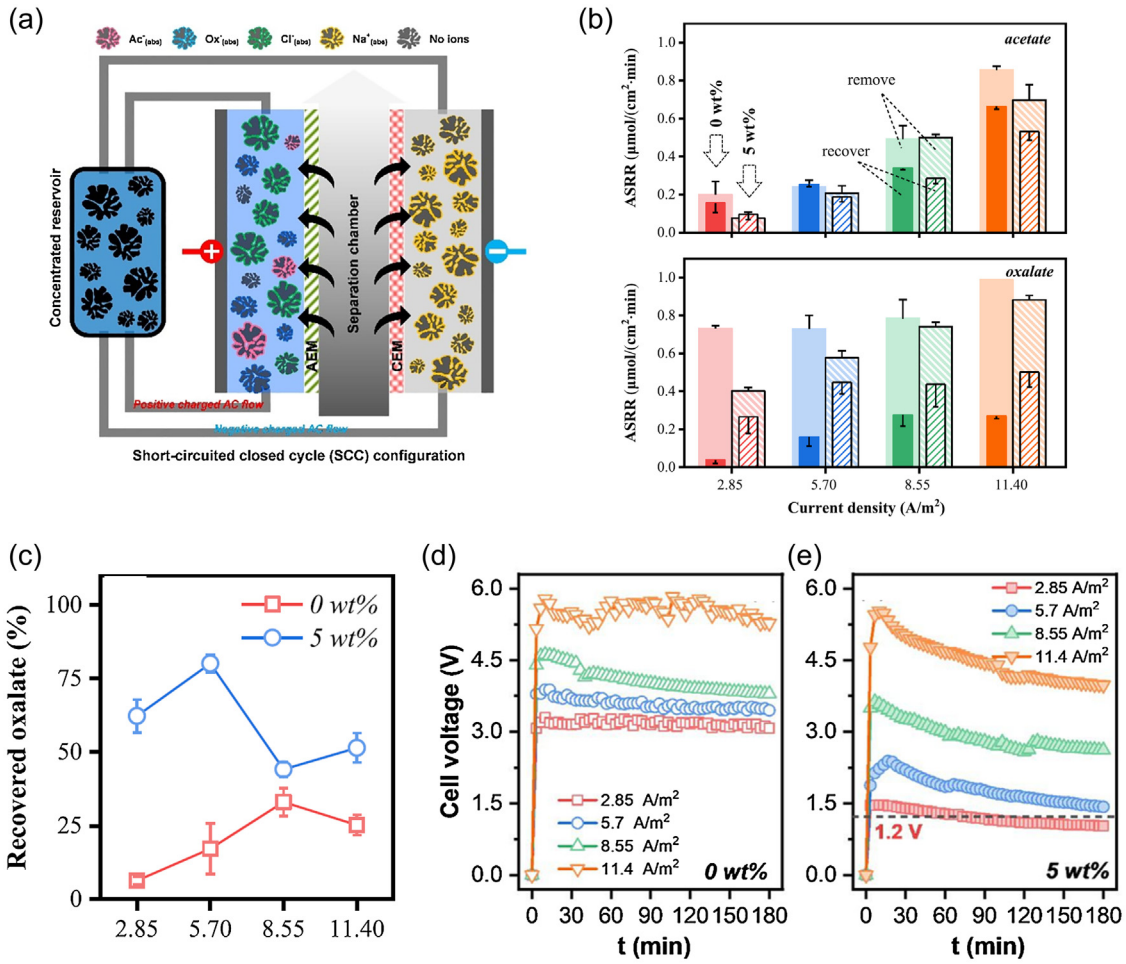

Fig. 7 – (a) Schematics of flow-electrode capacitive deionization (FCDI) and performance of organic acid recovery: (b) average salt removal rate (average organic acid recovery), (c) percent of oxalate recovery, (d) and (e) cell voltage for conventional ED model (0 wt%) and FCDI (5 wt% carbon contents). The figure is reproduced from Yu et al. (2021).

non-faradaic carbon adsorption is dominant over the water-splitting reaction or oxalate degradation (Fig. 7(e)). As a result, under optimal operating conditions (e.g., current density of 5.7 A/m^2), over 80% of both acetate and oxalate was recovered with a low energy consumption of 0.45 kW h/m^3 (Yu et al., 2021).

3.4.2. *Recovery of organic acids in juice and wine industries*

Tartaric acid is a natural constituent in most fruits, especially in grapes. It is often used as an acidulant in drinks, or an additive in pharmaceuticals and cosmetics (Vecino et al., 2020). During wine and juice production, however, tartrate needs to be partially removed for stabilization purposes (Andrés et al., 1997; Vecino et al., 2020). For instance, fermentation of alcohol decreases the tartrate solubility due to the presence of ethanol, resulting in undesirable precipitation in the bottles (Gonçalves et al., 2003). Thus, several studies have explored the valorization of the tartaric acid in winery downstream via electrodialysis (Andrés et al., 1997; Smagghe et al., 1992; Vecino et al., 2020). Recently, Vecino et al. (2020) recovered tartaric acid from distilled vinasses with electrodialysis. They proposed two-step electrochemical processes using ED for upconcentrating the potassium hydrogen tartrate, followed by BMED for acidifying the recovered tartrate. Note that conventional downstream recovery processes require more than 5 steps including separation of the solids and liquid fractions, precipitation of tartrate into calcium tartrate salts, then filteration, and finally recrystallization of the products as tartaric acid crystals. In this regard, electrochemical separation can lead to process intensification, by condensing the multiple steps down to two steps, thus improving modularity and sustainability. By using BMED, tartaric acid was successfully valorized (9900 ppm tartaric acid with 70% purity) from the distilled vinasses containing tartrate (3300 ppm) along with various salt contents such as sodium (370 ppm), potassium (2800 ppm), chloride (1640 ppm), phosphate (1560 ppm) (Vecino et al., 2020). Given that the global production of wine has exceeded 292 million hectoliters in 2018 (Vine and Wine, 2019), valorizing the winery downstream via the electrochemical technique is economically and environmentally viable with the intensified process for the recovery of tartaric acid.

3.4.3. *Selective biomolecule adsorption via electrosorption*

More recently, the design of molecularly selective interfaces towards value-added molecules has been explored for the selective electrosorption of organic acids and proteins (Fig. 8(a)). By leveraging the high affinity of the redox polymer towards oxyanions, poly(vinyl) ferrocene (PVF) has been successfully applied to recover diverse carboxylic acids and proteins with various isoelectric points and molecular sizes (Fig. 8(b) and (c)). PVF/CNT electrodes exhibited high uptakes and selectivity for both carboxylates and proteins. For instance, depending on the carboxylate structure, redox-

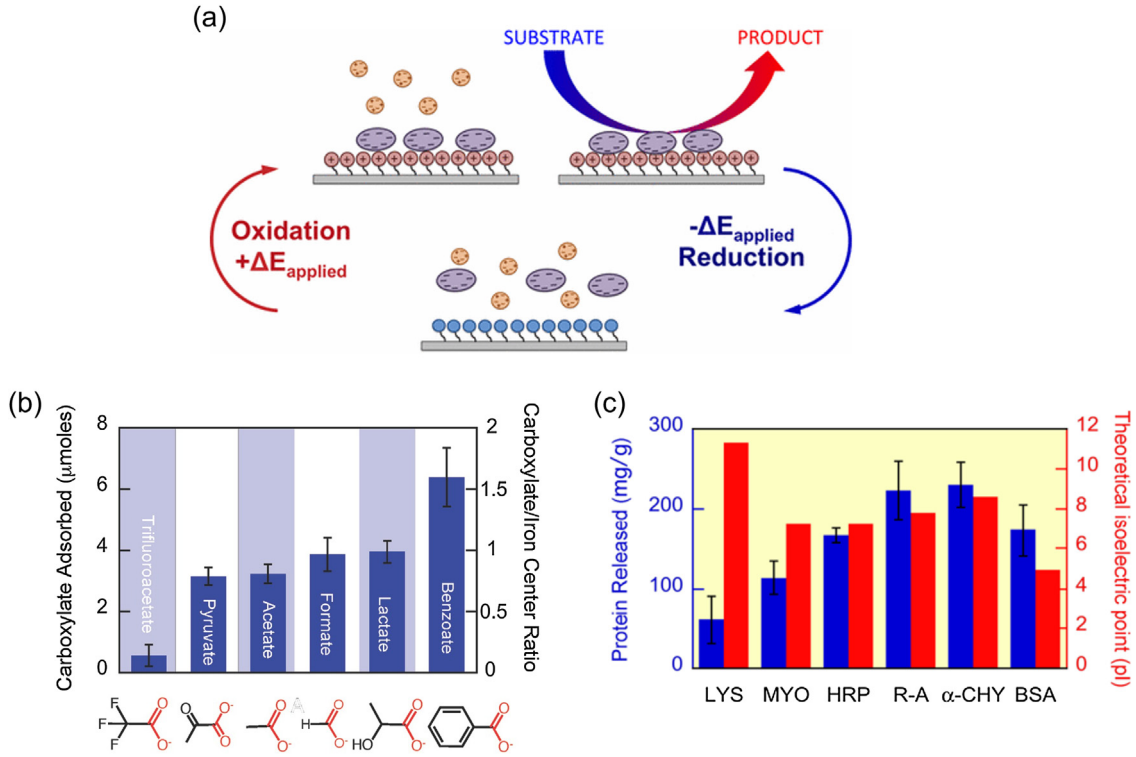

Fig. 8 – Selective electrosorption of biomolecules: (a) selective electrosorption based on redox–adsorbent oxidation through electrochemical control and adsorption capacity of (b) carboxylates and (c) proteins using the conducting polymer electrode (PVF/CNT). LYS, MYO, HRP, R-A, α-CHY, and BSA stand for lysozyme, myoglobin, horseradish peroxidase, ribonuclease-A, α-CHymotrypsin, and bovine serum albumin, respectively. Panels (a) and (c) are reproduced from Su et al. (2017a), Copyright (2017) American Chemical Society, and (b) from Su et al. (2016).

electrodes showed superior selectivity in both aqueous and organic solvents (Su et al., 2016). In addition, the system showed a remarkable uptake of >200 mg/g proteins over the wide range of sizes and charge distributions (Su et al., 2017a). Moreover, the recovered proteins and enzymes maintained their structures and catalytic activities (Su et al., 2017a). Interactions of these redox-electrodes with biomacromolecules involve several complex physical mechanisms such as the surface charge distribution and molecular size (Su, 2020a; Su et al., 2017a, 2016; Sun et al., 2016). The separation of value-added molecules with the interfacial affinity offers a delicate tunability towards target molecules, possibly expanding the application scope of redox-materials from the recovery of organic molecules to biocatalysis and potentially even electrochemically-responsive sensors.

4. Perspective: opportunities and outlook

The current review confirms that electrochemical approaches can be successfully applied to a wide range of food and bioprocessing. There has been growing attention to the electrochemical separations in the recovery of organic acids and biomolecules with diversified system architectures and electrode materials. Still, crucial challenges remain for both electrochemical membrane and electrosorption-based systems. For instance, ED systems often suffer from membrane fouling and extensive use of high-priced membranes (Grossman and Sonin, 1973; Tongwen, 2002). For electrosorption-based systems, there remains the need in understanding the complex binding interactions between electrodes and target species, especially biomacromolecules and active sites, and in applying these systems for practical downstream processes (Su, 2020a). Here we present opportunities and challenges for future research in electrochemical separations for bioprocessing and food manufacturing.

4.1. *Molecular-level understanding of complex interactions*

There remains untapped potential in electrochemical separation platforms for the selective recovery and fractionation of biomolecule mixtures. As demonstrated by the body of work covered in this review, electrochemical separation processes in food and biomanufacturing have typically been used for deionization. However, recent technological strides have been made in the adoption of electrochemical separation processes for the selective recovery and fractionation of biomolecules. For example, selective membranes have been synthesized and combined with electrochemical systems to separate chiral molecules (Xie et al., 2008). Besides understanding of selectivity mechanisms in electrosorption processes has advanced at a rapid pace, not only for ion separation (Zhang et al., 2020) but even allowing the capture and recovery of uncharged species (Mao et al., 2018). Nanostructured ferrocene-functionalized redox electrodes were shown to reversibly adsorb and release proteins through electrochemical potential swing (Su et al., 2017a). The affinity mechanism was hypothesized to depend on a complex combination of electrostatics, hydrophobicity, and surface charge distribution of the proteins. However, more in-depth elucidation of adsorption mechanisms, and structure function relationships of functional surfaces with proteins are needed. The structure and properties of biomacromolecules

are often more complex than ionic species, and therefore, more sophisticated multiscale computational modeling is often needed to understand their interactions. With growing understanding and even predictive control of molecular selectivity in electrosorption, we foresee tremendous potential in these electrochemical separation technologies for the selective recovery and fractionation of biomolecules.

4.2. *Engineering of electrochemical membrane systems*

As seen throughout the current review, ED technologies can play a key role in intensifying separation processes. Still, the ED system suffers from membrane-related challenges, originating from the cell assembly (e.g., stack resistance and concentration polarization) and materials property (e.g., fouling) (Al-Amshawee et al., 2020; Xu and Huang, 2008). Besides, the cost of ion exchange and bipolar membranes can be a major bottleneck for the large scale industrialization of electrochemical membrane systems. According to Greiter et al. (2002), to treat 11 m^3 of whey downstream with the ED system, approximately 530 cation and 530 anion exchange membranes (total membrane surface of 212 m^2) are needed, requiring an operating voltage of 225 V for half of the system. Besides, Ren et al. recently reported that the coexistence of amino acid and calcium contributes to the deterioration of the cation-selective layer of bipolar membranes (Ren et al., 2008). Therefore, achieving economic cell configurations is essential for the industrialization of the electrochemical membrane system for various separation processes. For instance, as discussed in Section 3.2.1 *Whey desalination via ED*, redox-mediated electrodialysis can lead to lower operating potential than the conventional ED system, reducing over 51% of the energy consumptions compared with the conventional ED systems (Kim et al., 2021b). In addition, the redox-mediated electrodialysis does not require additional ion-exchange membranes for scale-up; instead, a stack of electrodes and current collectors enables the treatment of a large volume of feed streams effectively (Kim et al., 2021b; Kim et al., 2020c). Since the high operating current in the ED system tends to increase the scale formation on the membranes, the use of redox couples in the separation process can mitigate membrane fouling (Grossman and Sonin, 1973; Huang et al., 2007). Moreover, there have been numerous reviews investigating the causes of membrane fouling, as well as prevention strategies (Langevin and Bazinet, 2011; Mikhaylin and Bazinet, 2016; Xu et al., 2012). The molecular size of the organic species can seemingly play a decisive role in membrane fouling. Species with molecules sizes between 200–700 Da can cause membrane clogging (Langevin and Bazinet, 2011). Operating an ED system with reverse polarity or pulsed electric current could also be a possible solution to reduce the membrane fouling (Langevin and Bazinet, 2011; Mikhaylin and Bazinet, 2016). Therefore, judicious engineering in cell architecture, operation optimization, and material design should be simultaneously carried out to develop efficient electrochemical systems practical industrial separations.

4.3. *Applications of electrochemical separation techniques in a non-aqueous environment*

The aforementioned applications of electrochemical methods in food and biomanufacturing have mainly focused on aqueous separations. Although industrial production of organic acids and proteins are mostly carried out in water, using non-aqueous environments (Desai et al., 2018) coupled with electrochemical methods may provide a fine control on the solubility and charges of biomolecules (Dimitrov, 2012; Schuur et al., 2019). Studies with ED systems have shown that the solubility of organic acids is significantly increasing in a mixture of water and organic solvents (Huang et al., 2007; Liu et al., 2015; Rottiers et al., 2017). Thus, finding optimal solvent mixture and conditions beyond water can broaden the scope of ED for the recovery of organic acids. Also, ultrafiltration membrane-coupled ED system can be applied in non-aqueous media to separate charged proteins or organic acids from relatively hydrophobic species, after extraction from the upstream production (Matsumoto et al., 2004; Molloy et al., 1999). Meanwhile, the addition and removal of salts as well as the judicious selection of organic solvents need to be investigated to improve the applicability of electrochemical techniques in non-aqueous applications. With organic solvents, low conductivity is likely to be one of the major issues, resulting in large voltage drops and consequently high energy consumptions (Jiang et al., 2013). Therefore, chemical pre-treatments such as charge modification of products, and addition of supporting electrolyte may be necessary to circumvent the low conductivity. Thus, before industrial implementation, extensive screening of organic solvents is necessary to meet all the needed requirements from a technical, environmental, health, and safety perspective (Rosinha Grundtvig et al., 2018). An ideal solvent should have process-friendly properties such as low viscosity and high vapor pressure, as well as electrochemical stability, low ecotoxicity, and biocompatibility for processes entailing biocatalytic reactions (Henderson et al., 2011; Prat et al., 2015; Tucker and Faul, 2016).

5. Conclusions

Electrochemical separations can be a promising sustainable technology for assisting with downstream bioprocessing and food manufacturing, especially for the recovery of organic acids and proteins. Notable advances include membrane-based electrochemical systems for the process intensification of value-added organic acid molecules via simultaneous recovery and acidification, as well as redox-active materials for electrosorption in which provide enhanced molecular selectivity, modularity, and material tunability. Still, there is a significant room for innovation and optimization for both electrochemical membrane and electrosorption-based systems. The development of inexpensive membranes and stable redox-electrodes is critical for enabling the scale-up and commercialization of electrochemical systems. Also, integration of these electrochemical separations with renewable energy can effectively reduce the overall carbon intensity of downstream processing. In sum, we envision steady advances in electrochemical separations will drive the translation from proof-of-concept electrochemical devices to practical industrial operations, and lead to more sustainable downstream processing for food and biochemical manufacturing.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge support by the National Science Foundation (NSF) under CBET Award #1942971, and support through startup funds by the Department of Chemical and Biomolecular Engineering, University of Illinois Urbana-Champaign.

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