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Electro-membrane separations in biotechnology

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Abstract:
Membrane processes are of crucial importance for downstream processing in biotechnology. This is due to their selectivity and the mild operating conditions, enabling to extract target products without damages caused by overheating and chemical agents. Besides the most spread membrane processes like ultrafiltration and reverse osmosis, electrodialysis is very important for removal and extraction of electrically charged products, i. e. anions of organic acids, some antibiotics, etc. The electrodialysis process can be organized in batch or continuous mode. On the other hand, in the electro-crossflow filtration, the transport of target solutes across the membrane is guided by two main driving forces, the transmembrane pressure and the electric potential. This combination enables various possibilities for more selective and efficient downstream processing in biotechnology. This chapter provides a brief overview of recent achievements of electrodialysis in selected bioproducts separations and recovery. A special focus, including original experimental data, is then given to electro-filtration, which is a powerful tool creating new opportunities for performing separations on the basis of both electric charge and particle size differences.

Keywords: aminoacids, bioactive albumin, donnan dialysis, downstream processing, electric field, electrodialysis, electro-filtration, lactic acid, microfiltration, organic acids, rabbit albumin, ultrafiltration

DOI: 10.1515/psr-2018-0063

1 Introduction

Membrane processes are essential for downstream processing in biotechnology, because of their selectivity and relatively mild operational conditions [1–5]. The latter are very important because of the thermal and chemical sensitivity of many bioproducts (e. g. proteins) and the high cost of biomass removal and target product(s) concentration by evaporation [6, 7]. The most spread membrane processes are ultrafiltration, reverse osmosis and electrodialysis. Whereas ultrafiltration is based on the permeation of molecules and particles with a defined size (lower than that of the membrane pores diameter) and, hence, leads to concentration of high- molecular mass products, reverse osmosis is based on the removal of the solvent (water) through a dense membrane by the application of mechanical pressure. On the other hand, Donnan dialysis is based on the transport of counter-ions (either positively or negatively charged) from one solution (i. e. fermentation broth) to another one, passing through ion-exchange membranes with oppositely charged fixed functional groups. The way to enhance this separation process is to apply an electric field. The process is called electrodialysis. The ions contained in the feed are attracted by the electrodes situated in the two adjacent compartments until their concentrations are increased in the concentrate compartment and the feed solution is exhausted. Cations permeate across cation-exchange membranes, but are retained by anion-exchange membranes, and vice versa. Thus, ions are accumulated in alternating cells, forming a concentrate solution, while the other cells are depleted of ions, thereby forming the so-called "diluate" solution. Electrodialysis is of special interest for separation and recovery of ionogenic products in biotechnology, as organic acids are such compounds.

The electrodialysis process can be organized in batch or continuous mode.

On the other hand, membrane filtration assisted by an electric field differs from electrodialysis, which is a purely electrically driven separation process using ion exchange membranes for ion separation. In the electro-crossflow filtration, the transport of target solutes across the membrane is guided by two main driving forces, the transmembrane pressure and the electric potential, which combination creates various possibilities for more selective and efficient downstream processing in biotechnology.

The present chapter first provides a brief overview of recent achievements of electrodialysis in selected bioproducts separations and/or recovery. A special focus, including original experimental data, is then given to electro-filtration, which is a powerful tool creating new opportunities for performing bioseparations on the basis of both electric charge and particle size differences.

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2 Examples for product recovery in biotechnology by dialysis membrane extraction

There are many examples in the literature about dialysis application in downstream processing in biotechnology. The prevalent majority with some exceptions [8, 9] is dedicated to anions extraction, e. g. organic acids recovery. The majority of them is focused on the extraction of a single carboxylic anion, but there are approaches for integrated processes allowing for simultaneous removal of more than one target ions, e. g. from fermentation broths [10–15] or hybrid downstream schemes involving with sorption processes [13].

The approach of pH control during electrodialysis for selective extraction of certain carboxylic anions from an acid mixture is of big interest [10, 14]. This process is sensitive to the acid strength, depending on the pK-values of the extracted acids and, therefore, the recovery of target acids could be tailored by maintaining or shifting the pH-value of the medium.

Selected examples of acid extractions by electrodialysis are considered below.

2.1 Volatile fatty acids (VFA)

This class of carboxylic acids are mainly products of anaerobic digestion of complex organic waste, like manure, straw and other lignocellulosic waste from agriculture used for the production of biogas. Their accumulation in the broth is undesirable because of the pH-shift beyond the optimum range for the methanogenic microbe metabolism in the consequent methane production. For this reason, different methods for VFA removal are considered [16, 17]. Electrodialysis has been tested as a separation process for VFA removal from fermentation broths [18–20]. Membrane separation coupled with pH gradient has been also successfully accomplished [14, 17].

Overall, separation of VFA by electrodialysis coupled with anaerobic digestion have been studied comprehensively during the last few years [19, 21–23].

2.2 Lactic acid

Lactic acid is one typical representative of the large-scale produced organic acids, due to its various applications, mainly as a monomer for biodegradable plastic manufacturing as well as in food industry and perfumery. Another important issue is the easy availability of relatively cheap substrates for its production, namely the whey-waste from dairy products production. The lactic acid accumulation during its production via fermentation leads to a pH drop and inhibition of the fermentation process, resulting into incomplete substrate utilization. That is why, different methods to avoid this undesirable effect have been proposed, including solvent ion exchange extraction [24], application of ion exchange resins [25–27] and electrodialysis [11, 12].

In the recent years, several studies on this process have been published. Lactic acid fermentation accompanied by electrodialysis to remove the lactic acid product-inhibitor is reported in [28, 29]. Processes involving membranes immersed in the fermentor in order to remove the lactic acid have been reported as well [30, 31].

An efficient downstream processing scheme of this fermentation including filtration, electrodialysis, ion exchange chromatography and distillation is presented in [32].

2.3 Aminoacids

The biotechnological manufacturing of aminoacids is a process of big importance for food industry, medicine, farmacy, animal feed, etc. The main advantage of the biotechnological way of production, in this case is the fact, that only the bioactive chiral compounds are produced. Downstream processing of aminoacids is a tricky procedure because of their amphoteric properties. One has to keep in mind that at certain pH-value (the so-called isoelectric point) the neutral molecules of each aminoacid turns into a zwitterion:

$$H_2N - R - COOH \leftrightarrow H_3N^+ - R - COO^-$$

Ion exchange and electrodialysis are the most spread treatment options in the downstream processing flow sheet [33]. There are several examples for aminoacid extraction from fermentation broth by electrodialysis in the recent years [34–37]. Those examples are for mono-sodium L-glutamate [34], methionine [35], L-phenylalanine [36] and L-threonine [37].

The selection of appropriate ion exchange membranes is limited to some adverse effects of the zwitterions on the membrane properties. That is why, dedicated membranes should be applied [38].

A number of reports are devoted to purification of aminoacids containing solutions from salts and sugars by ion exchange membranes [39–41].

Very interesting results for aminoacid separation by electrodialysis are reported by Kikuchi et al. in [42]. The application of appropriate cation-selective and anion-selective membranes enabled to separate glutamic acid, methionine and lysine from each other.

2.4 Inhibitor removal

Besides its major application for removal of carboxylic acids from fermentation broths [18, 24–27], electrodialysis can be used to remove other ionogenic inhibitors. A representative case is VFA removal in fermentative hydrogen production [43, 44]. The VFA separated by electrodialysis can be further converted into hydrogen as well.

There are some data on removal of inhibitors from lignocellulosic hydrolyzates by electrodialysis [45], recovery of succinic acid, which is an important biorefinery platform chemical [46–48].

2.5 Fuel cell applications

Other electrochemical applications of dialysis are associated with electricity generation in newly designed fuel cells [49–51]. Although there are still far from practical applications, the research efforts deserve encouragement.

3 Electrically enhanced crossflow membrane filtration as a separation tool in biotechnology

Attractive perspectives in the field of bio separation have been opened by coupling the cross-flow pressure-driven membrane processes with electrophoresis. The introduction of an electric field with sufficient strength and appropriate direction into the conventional dynamic filtration accelerates substantially the separation process.

In general, there is interaction between the surface charges of the membranes and the solutes in the feed solution/suspension which can lead to interference phenomena such as concentration polarisation, filter cake formation and membrane fouling at the membrane-solution interface. The combined electro-filtration process prevents to some extent the typical time-dependent permeate flux decline and improves substantially the separation selectivity. The special advantage of the electro-pressure-driven membrane processes lies in the soft anti-fouling effect; there is no need of additional shear forces to clear the membrane, it is safety to the membrane material and appropriate for treatment of sensitive bio systems. Apart from enhancement of the flux, the quality of the permeate resp. the product can be improved by applying an electric field [52].

To prevent the formation of cake on the membrane surface and membrane fouling, some specific conditions have to be fulfilled. The first one concerns the feed properties: the sign of the particles/colloids charge, pH value, feed concentration, conductivity and particle's electrophoretic mobility. The second one refers to the main process parameters (transmembrane pressure, feed flow rate, electric field strength and the type of the current flow) which have to be mutually adjusted in such way that the net particle migration is directed away from the membrane surface. In all cases, there is a critical electric field (the net particle migration velocity towards the membrane is zero) for every one of the systems to be treated which has to be determined experimentally. When the electric field strength exceeds the critical value, the electrophoretic velocity is greater than the convective flow and the concentration of dispersed materials is lowest near the membrane.

The performance of the electro-filtration process is primarily improved due to electrophoresis, the movement of charged particles or colloids relative to the liquid. In some cases, electro-osmosis (movement of the liquid relative to the stationary charged surface of the membrane or the filter cake) is found to be significant; therefore, the ζ-potential of the membrane is an important parameter too.

The electric field can be applied either across the membrane (with one electrode on either side of the membrane) or between the membrane and another electrode (the membrane itself is an electrode). The uniform distribution of the electric field along the membrane, which influences the process efficiency and the energy consumption during filtration, depends on the design of the electrodes and their location in the electro-filtration module. Wakeman and Tarleton [53] compared the performance of three module's configurations (plate, tubu-

lar and multi-tubular) and came to the conclusion that the tubular geometry offers the most effective use of electrical power, especially when the purpose is to prevent the membrane fouling.

The membranes can be made of electrically conductive or non-conductive materials. Usually, the anode is placed on the feed side because the particles are in most cases negatively charged. The best anode material is found to be titanium coated with a thin layer of a noble metal such as platinum [54]. The cathode, which could be the membrane support, is often made of stainless steel. Another alternative is the application of a membrane made of conductive material (metal or carbon) as an electrode [55]. It seems that one of the major restrictions in the commercial implementation of the electric enhanced technologies is the lack of suitable corrosion resistant and inexpensive electrode materials.

The application areas of the electro-assisted filtration include both "upstream processing" and "downstream processing" as well as the membrane reactors.

3.1 Applications of electro-microfiltration (EMF)

EMF of culture broth is studied by Matsumoto et al. [56] to control the selective permeation of protein solute (BSA) by using a flat MF membrane, DC (direct current), two platinum electrode plates and a cathode located on the permeate side. It was established that the feed pH value plays an important role in the separation process: at pH 7, BSA is rejected conditions (pH 3.5), BSA is charged positively and can pass the membrane.

Park [57] compared experimental results of the conventional microfiltration of haemoglobin with the cross-flow EMF. The permeate rate of EMF is found to be over 200% higher, due to the lower membrane resistance.

Hakoda et al. [58] applied an electro-microfiltration bioreactor (EMFBR) to treat a high-density culture of *Streptococcus lactis 527*, and studied the effect of the electric field on permeate flux and cell concentration. Inhibitory metabolites such as lactic acid is continuously removed from the fermentation broth during the bioprocess, whereas the cells are completely retained in the bio reactor. As a result, the cells of *S. lactis* in the EMFBR grew about 10 times as much as those of the conventional batch culture. The yield of cell against glucose and the maintenance coefficient increased substantially by application of an electric field.

3.2 Applications of electro-ultrafiltration (EUF)

Various aspects of the possibility for concentration of proteins by EUF have been investigated by Rios and Freund [59]. Based on results of experiments on electro-filtration of gelatine by using a tubular alumina membrane, the following general rules are stated (1) contrary to the purely pressure-driven UF, the tangential fluid velocity must be kept as low as possible; (2) there is optimal TMP that leads to a maximum permeate flux; (3) a special electric field setting technique is proposed in which the voltage has to be switch on before starting the fluid circulation.

Separation of BSA from polyethylene glycol (PEG), 20 kDa, using EUF is realised by Lentsch et al. [60]. In this case, the separation problem cannot be solved by a standard UF because BSA has about the same particle size as PEG. The BSA charge is highly dependent on the pH value of the feed solution: at pH 6.8, BSA can be repelled from the membrane whereas PEG is attracted towards the membrane by the electric forces. In this way, simultaneously transmission of PEG and retention of BSA in the retentate is reached.

To improve the performance of EUF by reducing the global membrane resistance, Mameri et al. [61] developed a module with a static deployed metal sheet as an anode which provokes turbulence near the membrane. The results show that the global hydraulic membrane resistance is reduced by half whereby the module is being more efficient for low cross-flow velocity and initial BSA-concentrations.

Oussedik et al. [62] developed a module with a static metal sheet as a turbulence promoter and an anode creating a pulsed electric field. The application of a pulsed electric field of approximately 700 V/m leads to an increase of the permeate flux by ~300%. However, the combination of a pulsed electric field and fluidized activated alumina in the feed solution (as a dynamic turbulence promoter) reduces this effect and an increase in the permeate flux of ~10% is only possible.

Zumbusch et al. [63] used alternating electrical fields as anti-fouling tool in EUF of biological suspensions. It is found that low frequency and high field strength yield the best results for electro-filtration of BSA. The effectiveness of the electric field increases with rising the conductivity up to the point where a limiting electrolytic current is reached. Moreover, increasing the protein concentration diminishes the effect of the electric field.

EUF of reverse micelles containing enzymes is studied in the first step of development of a special bioreactor for continuous enzymatic reactions [64]. It was found that the permeate flux increases with (1) increase in the AOT concentration or (2) decrease in the enzyme concentration. Both permeation flux and rejection of water

increased with increase in the applied electric field strength when the cathode is installed in the permeate side. Based on these results, a new type bioreactor reactor for continuous enzymic reaction is developed.

Hakoda et al. [65] applied EUF to enzyme starch hydrolysis and found that the filtration flux was much improved (with small loss of enzyme activity) when a buffer solution was not used in the bioreactor which decreases the electrical current.

Hakoda et al. [66] used a bio reactor for lipase-catalysed hydrolysis of triolein in an AOT reversed micelle system. An UF ceramic module of tubular type separates (rejects) the Aerosol AOT reverse micelles containing lipase from the continuous iso-octane phase containing the product. The enzyme containing RMs is retained in the reactor whereas the product solution is removed from it. The application of an electric field improves the productivity of oleic acid due to the increase in the permeate flux with increasing the electric field strength.

Turkson et al. [67] performed experiments on electro filtration of BSA with a rotating module and selected four dynamic membranes made of different materials (Zr(IV)oxide, calcium oleate, poly-2-vinylpyridine, and cadmium sulphide) as the most stable in the presence of a DC electric field for EF of BSA.

Enevoldsen et al. [68, 69] conducted crossflow EUF of five different industrial enzyme containing solutions and evaluated the process improvement in comparison with the conventional cross flow UF. For two amylases (amylase-F and amylase-S), the permeate fluxes increased 3–7 times, whereas in case of protease A and protease S, and lipase only minor flux improvement is achieved due to the low surface charge and availability of impurities. The pulsed electric field did not improve the flux. Greatest relative flux improvement is achieved at high enzyme concentration, therefore the EUF is found to be favourable as a final concentration step during UF of enzyme solutions. The conductivity is crucial for the feasibility of the EUF process, it has to be less than 2 mS/cm from an economical point of view.

UF is the most commonly-used method for the purification of whey protein. However, the required transmembrane pressure is relatively high (2–10 bar) with low limiting permeate flux. To reduce TMP and shorten filtration time without sacrificing product quality, an electro-microfiltration module is designed with Magneli Ti_4O_7/Al_2O_3 as the conductive membrane element [70]. During the EMF process, Ti_4O_7/Al_2O_3 serves as the cathode which possesses the same electrical charge as alpha-LA and beta-LG in the feed solution. The created electric field repels the whey proteins away from the membrane surface so that the components can be retained and concentrated. The designed EMF module provides a promising option for the concentration of whey protein in terms of both saved filtration time and acceptable product (retentate) quality.

3.3 Case study 1: Removal of BSA by MF in AC (alternating current) electric field

The present experimental study demonstrates the advantages of EMF for separation of bioactive albumin (BSA) from aqueous medium. The main purpose is to select suitable membranes and process conditions at which both permeate flux and composition remain constant over a long period of time.

A scheme of the electro-filtration set-up is shown below on Figure 1. The membrane module used was designed for flat sheet membranes (65 cm^2 effective surface) and two external electrodes. Due to the gas formation and other electrochemical reactions which may occur at the electrodes, external compartments are included on either side of the electrodes to avoid changes in the process streams. These compartments are separated from the retentate and permeate compartments by ion exchange membranes. The membrane module contains four chambers for the three streams: feed/retentate, permeate and electrode's rising electrolyte solution.

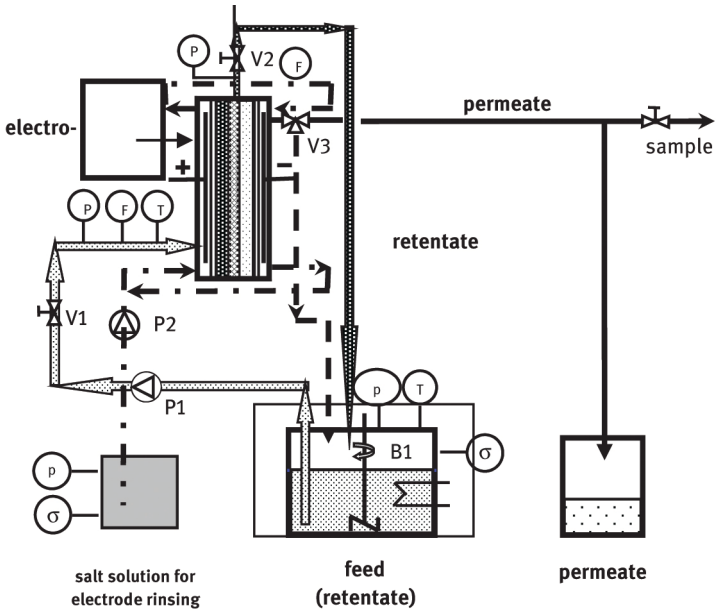

Figure 1: Experimental set-up for electro-filtration.

The ability of BSA to pass through different MF/UF membranes was compared using a feed containing 1 g/L BSA, feed flow rate of 300 L/h (linear velocity 2,2 m/s), and pressure at the outlet of the membrane cell of 2 bar; no current was applied. In Table 1, the permeate fluxes and rejection capacity of the tested membranes were compared. The *Celgard* UF-membranes (*C100 F and PS-200H*) showed the highest permeate fluxes (between ~254 and ~383 L/m^2.h); however, most of the BSA molecules were rejected by these membranes and remained in the retentate. The lowest rejection grade (~60%) showed the *Pall* MF membrane *Ultipor® NR* 0.2 µm. Therefore, this membrane was selected for the experiments in spite of the lower permeate flux.

Table 1: Permeate fluxes and BSA-rejection by different membranes.

Membrane	Time (min)	Rejection (%)	Permeate flux (L/m^2.h)
C100 F/Celgard	30	96.25	383.5
	60	95.92	364.0
UF-PS-	30	96.18	290.2
200 H/Celgard	60	96.30	254.0
Ultipor® NR/Pall	30	61.06	105.4
0,2 µm	60	60.59	107.3
Ultipor® NTG/Pall	30	85.57	118.3
0,1 µm	60	88.13	100.8
Ultipor® NT/Pall	30	86.37	94.2
0,1 µm	60	88.40	82.6

In Figure 2, the effect of the alternating electric field on the permeation flux is shown. At U =0 (no current), the permeate flux decreases gradually during the first 4 h from ~ 630 to ~290 L/m^2.h. In the same time, the electrically supported flux (U = 200 V, 1 s alternating electric field) remained substantially higher (~680 L/m^2.h) and almost constant (after 2 h stationary phase for the given experimental conditions).

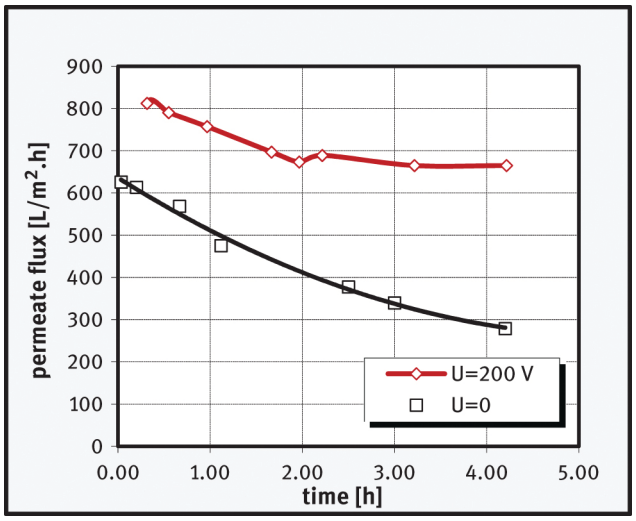

Figure 2: Comparison permeate fluxes at U = 200 V and U = 0.

In Figure 3, the influence of the initial BSA concentration on the permeate flux in combined electro-filtration is shown. At lower protein concentration (1 g/L), there is a linear dependence between permeate flux and voltage resp. electric field strength. The effect of the voltage is stronger at higher protein concentrations (5 g/L) in the feed: the permeate flux increases from 200 L/m^2.h (at U = 0 V) to ~650 L/m^2.h (at 200 V). The function permeate flux = f(voltage) becomes logarithmic one.

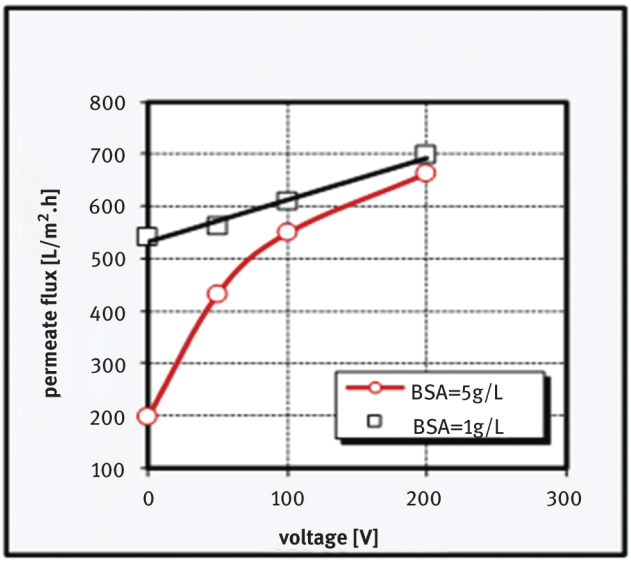

Figure 3: Comparison permeate fluxes at U = 0 ÷ 200 V.

The rejection of BSA by the selected membrane at different voltages (in the range from 50 V to 200 V) was determined. This effect was not very pronounced for the conditions studied: BSA 1 g/L; U_F = 0.32 m/s, p_{out} = 2 bar. The rejection/retention of BSA was found to decrease slightly from 3.4% (at 50 V) to 2.9% (at 200 V). This means that more than 97% of BSA-molecules permeates the membrane into the permeate side without to affect negatively the permeate flux.

3.4 Case study 2: EMF of rabbit albumin

The purpose of these experiments was to apply MF with an alternation electric field for treatment of a rabbit albumin solution with high conductivity (high content of ammonium sulphate). The analysis of the rabbit albumin solution by means of ZetaSizer gave important information about the particle size and ζ-potential as a function of pH.

Characterisation of suspension charges by means of the ζ-potential as a function of pH gave the isoelectric point at pH 5.35 (Figure 4). This means that the particles are negatively charged at pH > 5.35. The curve shows

that the most appropriate pH range is the light alkaline range because the ζ-potentials, resp. the electrophoretic mobility, are several times higher at these conditions comparing to the original pH value.

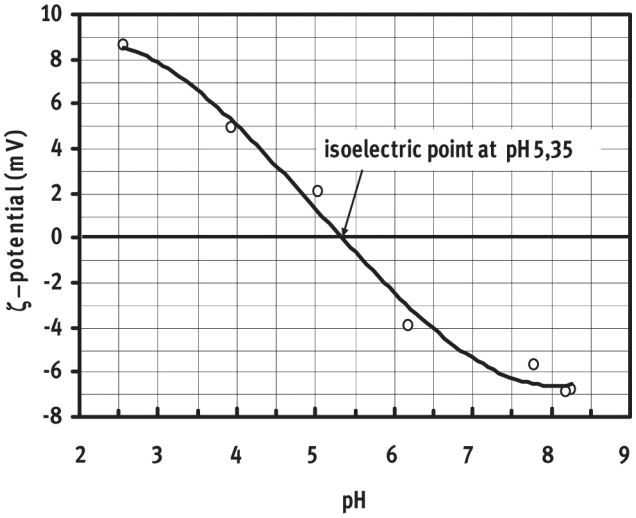

Figure 4: Effect of feed pH on ζ-potential of rabbit albumin solution.

The particle size was determined at three pH values: 4.08 (original solution), 2.91 and 7.27. It can be seen that at acid conditions the most of the particles have a size of 450 nm whereas at neutral pHs (7.27) most of the particles are two times smaller (Figure 5).

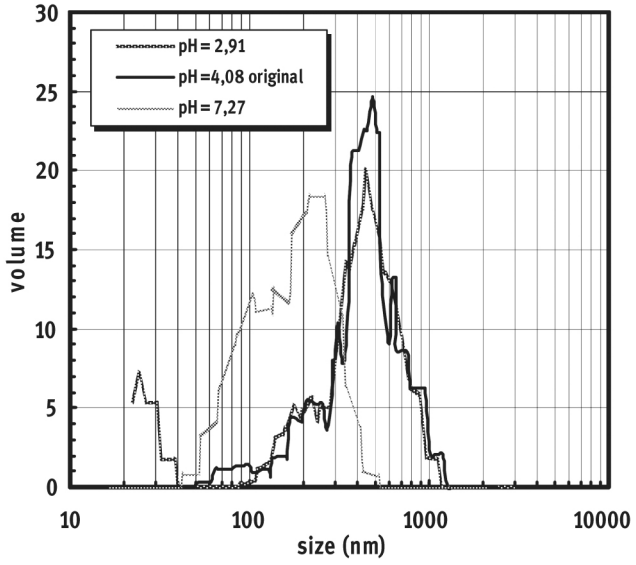

Figure 5: Particle size distribution as function of feed pH.

The electro-MF of the rabbit albumin solution was performed after adjustment of the pH value at pH ~ 7.2 by using an ammonium solution. The conductivity was found to be very high at 91 mS/cm. The EMF was performed at a voltage of 150 V and frequency of the pole alternation of 1 s. The electricity measured was 1.1 A (±0.2). During the conventional MF, a linear decline of the permeate flux with time was observed: for 80 min, the flux decreases from 900 to 735 L/h. At the same filtration time, the EMF gave a constant flux of 950 L/m^2.h, and the rejection of rabbit albumin was measured to be below 3%. The conclusion is that EMF can be successfully applied for filtration of the bio solutions with very high conductivities.

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