International Journal of Dairy Technology

SDT Society of Dairy Technology

doi: 10.1111/1471-0307.12884

REVIEW

A review of multistage membrane filtration approaches for enhanced efficiency during concentration and fractionation of milk and whey

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This review considers the impact of combining discrete membrane filtration configurations in a multistage or sequential configuration to improve processing performance, energy efficiency and component selectivity in dairy processes. The review focuses on the impact of multistage membrane filtration on (i) concentration processes, through the examination of fouling accumulation and its impact on flux and energy efficiency, and (ii) fractionation processes, whereby the yield/purity of dairy components is assessed. Observations from single-stage and batch microfiltration, ultrafiltration, nanofiltration and reverse osmosis processes reported in the literature are compared to the continuous multistage filtration processes common in commercial dairy installations.

Keywords Multistage membrane filtration, Dairy, Concentration, Fractionation.

INTRODUCTION: IMPROVED PROCESSING EFFICIENCY AT INDUSTRIAL SCALE

While for practical reasons the literature mostly addresses the application of single-stage filtration processes to dairy streams, milk processors employ nearly exclusively multistage sequential filtration processes to improve flux performance, reduce fouling and enhance membrane selectivity, when dealing with a stream as complex as bovine milk (Saxena *et al*. 2009; Meyer *et al*. 2017). In a multistage membrane filtration process, the retentate or the permeate of one step totally or partially feeds the next one in series or in parallel, thereby taking advantage of complementary membrane characteristics (cut-off, material, module configuration, *etc*.) and operating parameters (temperature, transmembrane pressure (TMP), cross-flow velocity, *etc*.). For instance, a combination of ultrafiltration (UF) → microfiltration (MF) → UF is typically applied to whey to produce whey protein concentrates or isolates whereby the first UF step concentrates the whey by a factor of 4–5 on a volume basis, thus reducing the feed volume delivered to the subsequent MF step. The MF (~0.1 μm) step retains residual casein, protein aggregates, fat globules and microorganisms, thus reducing fouling during subsequent UF of the MF permeate (Akpinar-Bayizit *et al*. 2009). Depending on the pore size of the MF membrane used, the retention of denatured/aggregated whey proteins may also provide the final protein concentrates with enhanced functional properties such as improved solution clarity in beverage applications. This concept as applied to whey is described by Carvalho and Maubois (2009) who reported a twofold increase in flux performance for a multistage MF-UF process compared to a single-stage UF as a result of upstream retention of fat globules. Per unit of plant footprint and membrane area, a UF plant represents a lower capital and operational cost than an equivalent MF plant, whereby the feed volume reduction from the initial UF step reduces the capital costs associated with the MF plant, and thus the process as a whole, in particular when utilising ceramic MF.

In some whey protein isolates manufacturing processes, a final NF or RO step may be applied to the UF retentate for concentration prior to spray drying, thereby removing the need for energy-intensive evaporation, thus preserving

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the native properties of whey proteins in the absence of a thermal treatment. Notwithstanding the lower rejection of NF relative to low molecular weight milk components compared to RO, the former may be employed as a less energy-intensive process (due to lower TMP requirements) downstream of a concentrating RO plant in order to increase the final dry matter of the concentrate prior to spray drying. Blais *et al*. (2021) examined the potential of a cascade of MF and RO for concentration of skim milk to improve process performance compared to RO alone. These authors did not observe improved RO performance associated with altered fouling accumulation when the system was operated at a low temperature (15°C). However, at higher temperatures (50°C), RO flux performance was improved by a factor of 2, associated more with a lower retentate viscosity and higher cross-flow velocity rather than the upstream retention of foulants by the MF step. It was hypothesised that the multistage process, whereby microorganisms were retained by MF, would prevent microbial growth during subsequent RO concentration at this higher temperature. More precisely, the 1.4 μm MF pre-treatment of skim milk was expected to retain mesophilic and thermoduric bacteria such as *Bacillus cereus*, *Salmonella typhimerium, Brucella abortus, Mycobacterium tuberculosis* and *Listeria monocytogenes* as well as non-pathogenic flora (Daufin *et al*. 2001; Carvalho and Maubois 2009; Mistry and Maubois 2017).

Two-stage membrane filtration processes have also proven to be an effective method for the recovery of dairy effluents, isolating valuable components in these streams. As such, a nanofiltration pre-treatment of dairy wastewater can be employed to retain residual proteins and lactose while yielding a low-osmotic pressure permeate, from which water is recovered by a sequential RO process (Vourch *et al*. 2005). To enhance permeate purification, multiple NF membranes (Mavrov *et al*. 2001) or RO membranes (Koyuncu *et al*. 2000) can be used in series, with the permeate of one feeding the next membrane, successively retaining the organic matter from the initial feed. White water recovery strategies such as this can be used to lower the volume and chemical/biological load of effluents discharged to water treatment and also feed into a sustainable water reuse strategy for a manufacturing site.

This review considers the impact of combining discrete membrane filtration configurations in a multistage approach to improve processing performance, energy efficiency and component selectivity in dairy processes. The challenge is to compare and contrast the observations from single-stage and batch filtration processes reported in the literature to the continuous multistage filtration processes common in commercial dairy installations. For instance, when translating lab-scale findings obtained in batch mode to industrial scale trials run continuously, attention must be paid to ensure that the typically longer operational cycles does not compromise product quality and food safety considerations. This review will address filtration processes employed to concentrate dairy streams whereby the role of MF, UF and NF on flux evolution and concentration dynamics are evaluated. In parallel, consideration will be given to the impact of these discrete membrane processes on selectivity in terms of purity and yield of valuable milk components. While other concentration or fractionation filtration processes have been described using emerging technologies such as charged membranes (Brisson *et al*. 2007; Arunkumar and Etzel 2013, 2014; Valiño *et al*. 2014; Arunkumar *et al*. 2016), the authors have restricted the scope of this review to neutrally charged membranes.

MEMBRANE FILTRATION PROCESSES EMPLOYED BY THE DAIRY INDUSTRY

Pressure-driven membrane filtration processes commonly used by the dairy industry can be broadly classified into four categories, according to pore size and rejection characteristics:

Microfiltration (MF) employs membranes with a cut-off of 0.1–10 μm in order to remove fat globules, somatic cells, vegetative bacteria or spores and large protein aggregates from dairy streams, or for the fractionation of large macromolecules (e.g. enrichment of casein micelles and depletion of serum proteins prior to cheese-making) (Carvalho and Maubois 2009). Typical TMP varies from 0.03 to 0.2 MPa (Bhattacharyya *et al*. 1992).

Ultrafiltration (UF) typically uses membranes with a cut-off of 1–800 kDa operated within a TMP range 0.1–1 MPa (Cui *et al*. 2010). It is primarily used for the production of protein concentrates or isolates from milk/whey (e.g. whey protein concentrates) from which salts, lactose, water-soluble vitamins, non-protein nitrogen and other soluble solutes are removed (Gésan-Guiziou 2007). Furthermore, it can be employed to standardise the total protein and fat content of cheese/drinking milk (Carvalho and Maubois 2009). The milk/whey permeates generated during UF are typically used for standardisation purposes or for subsequent lactose production (Atra *et al*. 2005).

Nanofiltration (NF) uses membranes with a typical cut-off of 150–700 Da that are applied for the concentration and partial demineralisation of whey or milk streams; whereby, dissolved mineral salts are removed inversely proportional to their valence (Mistry and Maubois 2017). The demineralisation capacity is counterbalanced by the partial permeation of low molecular weight components such as lactose, dependent upon their concentration in the retentate. Nanofiltration can concentrate skim milk or whey to 20–22% dry matter in tandem with 25–50% partition of monovalent ions, which can be increased to 90% through diafiltration of the retentate. Partial demineralisation of milk/whey permeates by NF increases lactose crystallisation efficiency and can reduce the hygroscopicity of resulting powders (Daufin *et al*. 2001). The operating pressures of this process are typically 1–3 MPa (Cui *et al*. 2010).

Reverse osmosis (RO) uses membranes operated at pressures of 3.5–10 MPa (Cui *et al*. 2010) that only allow water

to permeate (Carvalho and Maubois 2009). This process is used to concentrate milk/whey up to ~27% dry matter (Gésan-Guiziou 2007) before evaporation in order to reduce the overall energy consumed during milk powder production. RO performance is limited by the osmotic pressure and viscosity of the retentate at higher dry matter contents, which reduces cross-flow velocity and leads to fouling build-up over time.

CONCENTRATION PROCESSES

Performance gains by MF pre-treatment

Prior to milk powder production by spray drying, in general, milk is concentrated by evaporation. An RO installation can be added at the front end of the process, improving energy efficiency during milk concentration (Fox *et al*. 2010). As reported by Blais *et al*. (2021), the energy efficiency of the concentration of skim milk can be further improved by the addition of an MF (1.4 μm) treatment prior to RO (Table 1). The authors hypothesised that the upstream retention of microorganisms (and spores) from skim milk by MF (see Table 4), as reported by Elwell and Barbano (2006), allows the subsequent RO step to be carried out at 50°C as opposed to normal operational temperatures of <10°C without compromising microbiological safety. This increased RO flux due to a lower retentate viscosity, with a ~ 57% reduction in energy usage per unit volume of water removed compared to a single-stage RO process operated at 15°C.

Similarly, retention of microorganisms during MF (0.2 μm) pre-treatment of mozzarella whey allowed Rektor and Vatai (2004) to subject the resulting permeate to NF (400 Da) at temperatures ranging from 30 to 50°C (Figure 1). Compared to subjecting whey directly to NF at 40°C, the retention of ~67% of proteins from whey by the initial 0.2 μm MF step (see Table 4) increased the subsequent NF flux by a factor ~3 for volume concentration factors (VCF) up to 4.5, most likely due to a lower retentate viscosity due to the lower protein content, and possibly due to altered fouling accumulation. The retention of 19.5% lactose from whey in the initial 0.2 μm MF indicates that the VCF was in the range 4–5, although it was not reported. The authors also evaluated the performance of the MF permeate during subsequent RO at 30°C and observed a flux increase of 20% (from ~10 to 12 L/m^2/h) at a VCF of 2 compared to subjecting the whey directly to RO. These results are in line with observations of Blais *et al*. (2021) who noted a marginal flux improvement when a combination of MF and RO was applied to skim milk at low temperatures, where osmotic pressure has a more significant effect on RO performance than viscosity at lower concentration factors.

Table 1 Process parameters used in studies focusing on the concentration of dairy streams

Reference	Feed type	Filtration process(es)	VCF	TMP (MPa)	Temperature (°C)
Blais *et al*. (2021)	Skim milk	MF (1.4 μm) using tubular ceramic modules, in series with RO using spiral-wound composite polyamide modules	2–11	0.210 (MF), 2.92 (RO)	50 (MF), 15 or 50 (RO)
Rektor and Vatai (2004)	Mozzarella whey	MF (0.2 μm) using hollow-fibre or ceramic multitube modules, UF (100 kDa) using spiral-wound modules, NF (400 Da), RO using plate-and-frame modules	2–7.5	0.2 (MF), 2.5–3 (NF), 4 (RO)	30–50 (NF), 30 (RO)
Meyer and Kulozik (2016)	Sweet whey, skim milk, UF permeate (RO)	UF (10 kDa) using spiral-wound modules in series with RO using spiral-wound polyamide modules	3.8–5.8	0.3 (UF), 4 (RO)	10 (UF and RO)
Patil *et al*. (2014)	Whey protein isolate solution	UF (60 kDa) using flat-sheet modules	–	0.066–0.1	25
Atra *et al*. (2005)	Whey	UF (6–8 kDa) using polyvinil-difluoride or polyethersulfone modules	~5.5	0.1–0.5	30/50
Luo *et al*. (2011)	Diluted skim milk	UF (5–30 kDa) using polyethersulfone or regenerated cellulose modules, in series with NF (90–400 Da) using polyamide modules	5	0.1–0.4 (UF), 0.8–3.7 (NF)	25
Yorgun *et al*. (2008)	Curd and white cheese whey	UF (20 kDa) using polyethersulfone modules, NF (<200 Da) using polyethersulfone, polyamide or polysulfone modules, RO using polyamide–urea modules	1.7–8	(UF), 0.5–0.8 (NF), 1.2 (RO)	–

VCF, volume concentration factor; TMP, transmembrane pressure; MF, microfiltration; UF, ultrafiltration; NF, nanofiltration; RO, reverse osmosis.

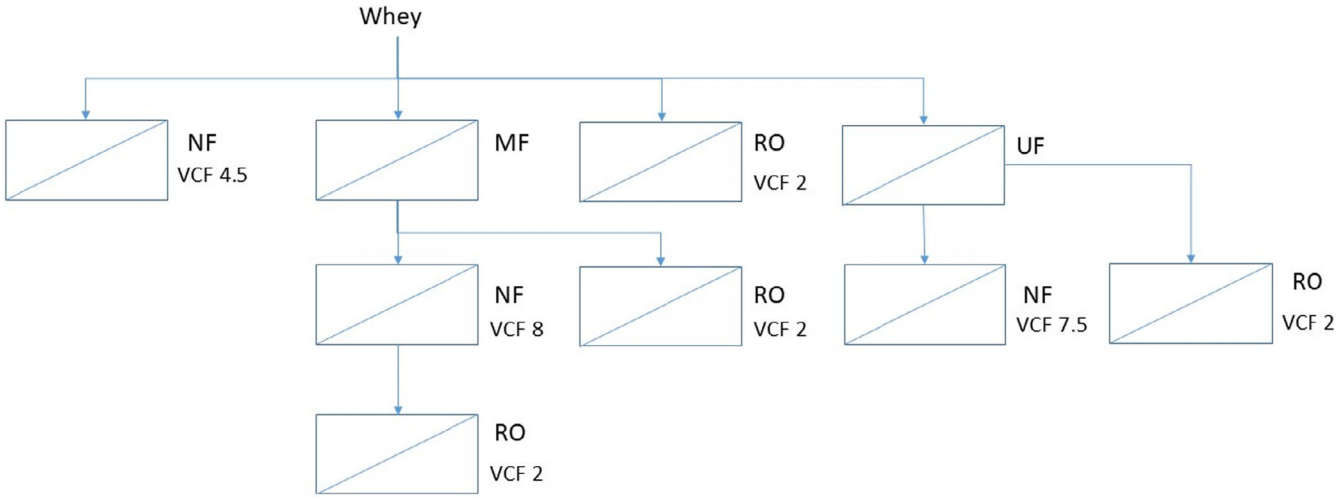

Figure 1 Cascade filtration process for mozzarella whey reported by Rektor and Vatai (2004).

Performance gains by UF pre-treatment

In order to assess the efficacy of a UF (10 kDa) pre-treatment to reduce feed osmotic pressure, which is seen as the main limitation to RO performance, Meyer and Kulozik (2016) compared the RO flux obtained in batch mode using three different feed solutions: skim milk, sweet whey and UF permeate (originating from clarified sweet whey). Due to the upstream protein retention of the UF treatment (see Table 4), the osmotic pressure and viscosity of the resulting protein-free serum was lower than that of the other feed solutions, allowing a VCF of 5.8 to be reached during subsequent RO of the ultrafiltrate compared to 3.8 or 5 during RO of skim milk or sweet whey respectively. Furthermore, the RO flux for UF permeate increased by a factor of 1.3 and 3.4 at a VCF of 3 compared to sweet whey and skim milk respectively. It should be noted that the UF process was performed in batch mode and did not account for the progressive introduction of foulants, or their accumulation during continuous filtration. Meyer and Kulozik (2016) stated that mixing of both UF and RO retentates prior to evaporation/drying improved the efficiency of production of a recombined skim milk, or sweet whey concentrate. When directly comparing these observations to conventionally used concentration factors prior to evaporation, the benefits of the sequential UF–RO process are limited in terms of overall VCF and flux, considering the relatively low concentration factors applied during commercial RO of milk/whey. In corollary, the complexity of running two discrete membrane processes in series, coupled with the additional capital and operational costs are challenged considering that the same concentration outcome can be achieved by RO alone.

Similarly, to reduce the osmotic pressure of mozzarella whey, Rektor and Vatai (2004) subjected this stream to a UF (100 kDa) treatment before either NF (400 Da) or RO of the resulting UF permeate (Table 1). As expected, the UF treatment retained all the fat present in the original whey, as well as 75% of the proteins and 41% of the lactose (Table 4), with the latter retention due to the relatively low concentration factors applied. The protein retention <100% can be explained by the permeation of individual whey proteins smaller than 100 kDa (e.g. α-lactalbumin and β-lactoglobulin) as well as to the presence of non-protein nitrogen compounds, in the permeate, affecting the measured protein concentration. Due to the upstream solute retention and lower feed osmotic pressure and viscosity, a VCF of 7.5 was reached during NF of the UF permeate compared to 4.5 for the original whey, with a concomitant ~5-fold increase in flux. The flux improvement was significantly lower during concentration of the UF permeate by RO, increasing by a factor of 1.6 compared to direct RO of the whey at a VCF of 2. This may be associated with the higher rejection efficiency of RO membranes, whereas the larger pore size NF membrane has a lower rejection coefficient for monovalent ions and other low molecular weight milk components, making the membrane less susceptible to osmotic pressure differentials. As the NF was operated at a 10°C higher temperature compared to the RO process, this alone may account for a significant proportion of the flux improvement observed.

Flux evolution is dependent upon feed composition, membrane cut-off, plant configuration, temperature, and batch or continuous operation with many configurations reported among the studies reviewed. Patil *et al*. (2014) observed that reducing the ionic strength of a whey protein isolate suspension (5 vs 50 mM NaCl at pH 7.2) resulted in a higher flux (45 vs 35 L/m^2/h). The authors suggested that the resulting change in charge affected protein–membrane

interactions. When subjecting whey to a batch UF (6–8 kDa) process, Atra *et al*. (2005) observed that increasing transmembrane pressure from 0.1 to 0.5 MPa resulted in an average flux increase of 40% within a VCF range 1–5.5, although it is difficult to extrapolate this to a continuous process due to the relatively low feed mass involved (25 kg). Nevertheless, improved flux performance relative to increasing TMP is often short lived above a so-called critical flux value, regardless of VCF, as performance gains are soon counteracted by increased concentration polarisation (fouling) at the membrane surface. In parallel, these authors observed a decrease in total protein rejection of 4.3% at the highest transmembrane pressure up to a VCF of 5, after which fouling accumulation and increased solution viscosity increased protein rejection. This can be further influenced by processing temperature whereby increasing the operating temperature from 30 to 50°C resulted in a ~ 50% flux increase, linked to a reduced viscosity and higher diffusivity of soluble components (Atra *et al*. 2005). Similarly, increasing the recirculation flow rate, and thus cross-flow velocity, from 100 to 400 L/h resulted in a 100% increase in flux linked to altered fouling resistance at the membrane surface.

A cascade UF/NF process has also been investigated to improve the efficiency of white water recovery during treatment of wastewater from dairy processes (Luo *et al*. 2011). Using a model dairy wastewater (skim milk diluted by a factor 10) and UF membranes with cut-offs ranging from 5 to 30 kDa, these authors achieved retention of 99.46–100% of the proteins from the dairy wastewater, while permeating most of the lactose and salts (Table 4). The protein retention of 99.46% was obtained with the membrane cut-off of 30 kDa thereby allowing the permeation of small whey proteins; the permeate obtained from the 10 kDa membrane was selected to feed subsequent NF. The NF treatment retained most of the soluble components at slightly varying selectivity dependent upon TMP and VCF. Under conditions of constant flux, the TMP of this NF process was compared to that of a single-stage NF directly concentrating the model wastewater. While the TMP for the NF step in the cascade process remained constant (~0.8 MPa) over 120 min of filtration, it increased to 3.57 MPa in 12 min for the single-stage NF due to foulant accumulation and increases in viscosity within the filtration plant.

Performance gains by NF pre-treatment

To reduce the biological/chemical oxygen demand of process effluents discharged to water treatment, Yorgun *et al*. (2008) subjected cheese whey to either single-stage UF (20 kDa, VCF 8), NF (<200 Da VCF 4), RO (VCF 1.7) or a cascade of NF/RO (VCF 6.5/1.6) processes (Table 1). They observed that 96% of total protein was retained by the overall cascade NF/RO process compared to 78, 90 or 94% for single-stage UF, NF or RO, respectively (Table 4). Atra *et al*. (2005) retained 93–98% of total proteins from whey subjected to a UF (6–8 kDa) process, using similar transmembrane pressures (0.3–0.5 MPa) to those used by Yorgun *et al*. (2008) (0.3 MPa). The considerably higher retention from Atra *et al*. (2005) may partially be attributed to these authors not differentiating between crude (including non-protein nitrogen (NPN)) and true protein (Mariotti *et al*. 2008), thus overestimating protein content as highlighted by Yorgun *et al*. (2008).

Rektor and Vatai (2004) subjected an MF permeate (originating from mozzarella whey) to a cascade NF/RO process, whereby the NF permeate was used as feed for the subsequent RO step (Table 1). These authors reported a flux increase by a factor 1.6 or 1.8 for the cascaded RO step at a VCF of 1.5 or 2, respectively, compared to those obtained for direct concentration by RO. The higher flux was expected as the NF process retained most solutes with the exception of a proportion of the monovalent ions and non-protein–nitrogen, resulting in a very low osmotic pressure during RO. Considering the high energy consumption of the RO process when concentrating feed at high osmotic pressures, the addition of an NF pre-treatment may be beneficial as part of a concentration and water recovery process in commercial installations.

FRACTIONATION PROCESSES

Membrane filtration presents several advantages over conventional thermal and mechanical concentration processes (e.g. evaporation, decantation and centrifugation) such as separation of components in their native form, without deleterious effects associated with shear/temperature (Daufin *et al*. 2001). Membrane filtration technology allows for a clean label approach to fractionation of dairy components since it does not require the addition of any chemical (e.g. an enzyme or processing aide).

One of the widest applications of membranes is in the manufacture of whey fractions including concentrates and isolates, for use in infant formulae and sports nutrition products, where nutritional and functional properties can be tailored to end-user requirements. Whey ingredients allow reformulation of bovine milk to closely reflect the whey/casein ratio found in human milk (fluctuating between 80/20 and 50/50 in early and late lactation, respectively (Martin *et al*. 2016)) rather than the 20/80 ratio of these proteins in bovine milk (Lara-Villoslada *et al*. 2005). More recently attempts have been made to selectively separate individual bovine milk components such as α-lactalbumin, immunoglobulin G (IGG) and phospholipids to further humanise infant nutrition products.

Caseins and whey proteins

Caseins and whey proteins are valuable functional and nutritional ingredients within the food industry which can be successfully isolated by membrane filtration (Carvalho and Maubois 2009). Microfiltration in both ceramic and

polymeric formats has emerged as the technology of choice for casein/whey separation with ongoing research focused on purity, and overall filtration efficiency. The following sections will assess the performance gains when using a cascade of MF, UF or NF, correlating membrane characteristics and operating parameters (where possible) to fractionation outcomes; with the filtration operational parameters of the studies reviewed reported in Table 2.

Improved selectivity by MF

Prior to cheese-making, Nelson and Barbano (2005) subjected skim milk to a three-stage cascade filtration process to concentrate caseins and remove whey proteins while maintaining the concentration of lactose, salts and non-protein nitrogen in the retentate similar to that of milk. Initially, skim milk was subjected to MF (0.1 μm) at 50°C to preferentially isolate whey proteins, lactose and salts from casein micelles. The MF permeate was then subjected to UF (10 kDa) at 50°C and the UF permeate was used as a diafiltrant during subsequent MF processing. The cascade filtration process successfully partitioned 95% of the serum proteins from the original skim milk (see Table 4) while the casein content of the MF retentate was concentrated 3.1 times compared to that of the starting material. When subjecting skim milk to MF (0.1 μm), Hartinger *et al*. (2019) obtained a higher transmission of both α-lactalbumin and β-lactoglobulin at 10 compared to 50°C when a steady flux was reached (53 and 45% at 10°C vs 50 and 38% at 50°C, respectively) (Table 4). These authors also observed that β-lactoglobulin transmission decreased by a factor > 11 with increasing transmembrane pressure (from 0.05 to 0.3 MPa), attributable to deformation, accumulation and compaction of casein micelles at the membrane surface. By subjecting raw skim milk to a slightly larger membrane cut-off (0.14 μm) at 50°C, Heidebrecht *et al*. (2018) retained more than 99% of intact caseins from milk, and observed increasing rejection coefficients for β-lactoglobulin and immunoglobulin G, at 35% and 50% for 0.1 and 0.2 MPa TMP respectively (Table 4). At higher TMP, the transmission of whey proteins progressively decreased due to either an increased accumulation at the membrane, or a pore plugging effect. It is clear that there is a critical relationship between the application of sufficient TMP to allow protein convection towards and through the membrane, and accumulation of a fouling layer which acts as a secondary filtration layer of lower permeability. The manipulation of VCF, TMP and diafiltrant, such as use of UF permeates to maintain ionic equilibrium, are all strategies to maximise whey protein partition during MF (Nelson and Barbano 2005). To compare protein functionality in whey obtained from either MF of milk, or from UF

Table 2 Process parameters used in studies focusing on milk protein fractionation

Reference	Feed	Filtration process	VCF	TMP (MPa)	Temperature (°C)
Nelson and Barbano (2005)	Pasteurised skim	MF (0.1 μm) using ceramic modules, in series with UF (10 kDa) using plate-and-frame polysulfone modules	3–20	0.023–0.028 (MF)	50
Le Berre and Daufin (1998)	Raw milk	MF (0.1 μm) using ceramic modules	2	0.3	50
Hartinger *et al*. (2019)	Skim milk	MF (0.1 μm) using spiral-wound polyvinylidene fluoride modules	–	0.05–0.3	10 / 50
Heidebrecht *et al*. (2018)	Raw skim milk	MF (0.14 μm) using ceramic modules	–	0.1–0.2	50
Britten and Pouliot (1996)	Raw milk Cheddar cheese whey	MF (1.4 μm), in series with MF (0.1 μm), in series with UF (10 kDa) using hollow-fibre polysulfone modules	16	0.12	50
Cheang and Zydney (2004)	Whey protein isolate enriched with 0.1% bovine serum albumin	UF (30 or 100 kDa) using composite regenerated cellulose modules	–	–	–
Almécija *et al*. (2007)	Clarified acid whey	UF (300 kDa) with ceramic modules	5	0.1	30
Patil *et al*. (2014)	Whey protein isolate solution	UF (60 kDa) using flat-sheet modules	–	0.066–0.1	25
Atra *et al*. (2005)	Whey, batch mode	UF (6–8 kDa) using flat-sheet modules	~5.5	0.1–0.5	30/50

VCF, volume concentration factor; TMP, transmembrane pressure; MF, microfiltration; UF, ultrafiltration; NF, nanofiltration; RO, reverse osmosis.

of cheese whey, Britten and Pouliot (1996) subjected raw milk to sequential MF treatments (1.4 μm and 0.1 μm) followed by concentration of the resulting MF permeate by UF (10 kDa) (see Table 2). In parallel, cheese whey was directly concentrated by UF (10 kDa). The authors observed an overall higher quality in the whey proteins produced by MF of milk compared to those produced by UF of cheese whey due to: i) the absence of degradation products from the starter culture and the upstream retention of fat by MF, which increased whey protein purity, ii) microorganism retention by MF allowed a milder heat treatment to be performed after the UF process thereby preserving native protein structures and iii) better gelling and foaming properties as well as a higher solubility.

When subjecting raw or heat-treated skimmed milk to MF (0.1 μm) at 50°C, Le Berre and Daufin (1998) retained 99 and 84% of the lactoferrin (77 kDa) and lactoperoxidase (77.5 kDa) present in milk respectively (Table 4). With increasing ionic strength of the feed (from 0.08 to 0.97 M) by addition of 0.92 M NaCl, lactoferrin and lactoperoxidase retention decreased to 49 and 73%, respectively, highlighting the influence of ionic conditions on protein partitioning. When using MF pore sizes of 0.14 or 0.20 μm for the partition of skimmed colostrum, Gosch *et al*. (2013) retained >98% of caseins, while lactoferrin retention was 73–78% and 69% for 0.14 and 0.20 μm MF membranes respectively. The authors reported that lactoferrin purity was higher in the 0.20 μm than in the 0.14 μm MF permeate, with the retention of 89% of immunoglobulin G in the former case compared to 75–84% in the latter. Further optimisation of this process may include additional downstream cascaded filtration steps to isolate whey protein fractions of interest. A MF (0.1 μm) pre-treatment at high ionic strength that removes caseins and immunoglobulin G while permeating lactoferrin and lactoperoxidase could be coupled with a sequential MF step at lower ionic strength to selectively retain lactoferrin and lactoperoxidase while allowing other whey proteins to permeate.

Improved selectivity by UF

Cheang and Zydney (2004) compared the yield and purity of α-lactalbumin and β-lactoglobulin obtained when subjecting a solution of whey protein isolate (enriched with bovine serum albumin) to a two-stage UF with diafiltration, operated in batch mode, using either a 100 kDa followed by a 30 kDa membrane, or in the reversed order (Figure 2). These authors observed retention of 0% α-lactalbumin and 22% β-lactoglobulin from the initial feed solution using a 100 kDa UF step (Process 1). When the permeate was further processed using a 30 kDa UF, ~30% of the overall β-lactoglobulin and 5% of the α-lactalbumin were retained by the membrane (Table 4). In the second process, nearly all of the β-lactoglobulin was retained by the 30 kDa UF module and 10% of the α-lactalbumin, yielding a permeate with an α-lactalbumin purity 10-fold higher than that of the feed. Subsequently, the 100 kDa UF module retained 30% of the β-lactoglobulin, yielding a permeate with a four-fold higher purity compared to the initial feed. The authors retained >90% of bovine serum albumin in the 100 kDa UF step of process 1; however, the purity was relatively low due to a concomitant retention of β-lactoglobulin. It should be noted that the levels of transmission of whey proteins reported by these authors are not typical for UF.

Patil *et al*. (2014) proposed a cascaded UF (60 kDa) process using three identical membrane modules operated within a TMP range 0.066–0.1 MPa in order to isolate α-lactalbumin from a whey protein isolate solution (Figure 3). The final product stream is the cumulative permeate obtained from the three UF processes connected in series, making use of the sequential rejection characteristics of the membrane to optimise recovery of the component of interest. While the TMP of modules 1 and 2 operated at 0.1 MPa, module 3 could only achieve a maximum TMP of 0.066 MPa due to volume constraints associated with the lab-scale process design. Despite the challenges encountered by the authors, the cascade filtration process yielded an α-lactalbumin recovery of ~80% with a ratio of product to

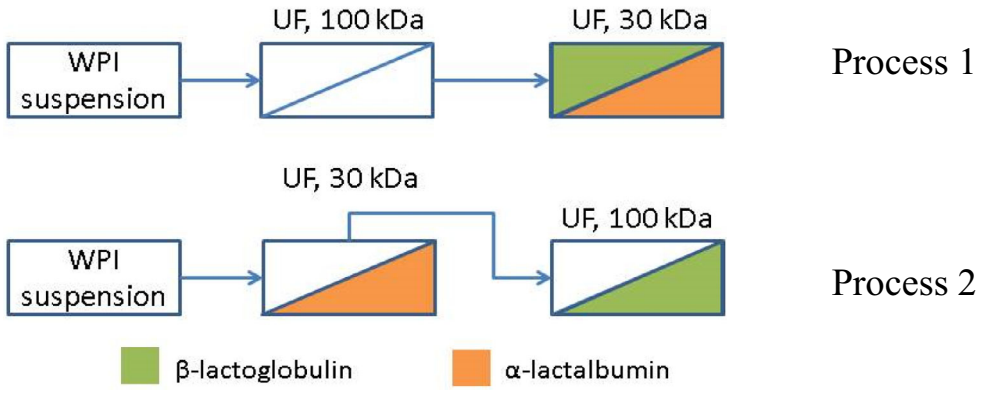

Figure 2 Isolation of α-lactalbumin and β-lactoglobulin from a whey protein isolate suspension using a two-stage batch UF process (Cheang and Zydney 2004).

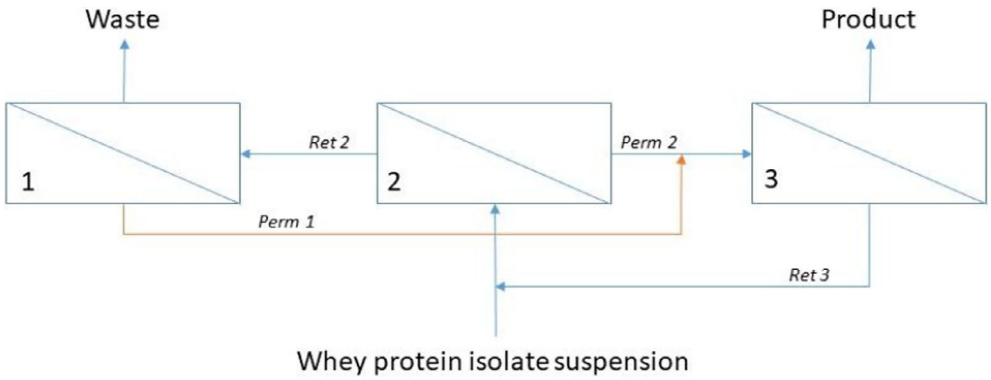

Figure 3 Cascade UF process described by Patil *et al*. (2014).

waste of 16:1. The partitioned α-lactalbumin fraction had a purity of ~70% on a protein basis. To maximise product recovery (although potentially at lower purity), the authors suggested reducing the membrane surface area of module 3 coupled with operation at a higher TMP.

The observations from Patil *et al*. (2014) were similar to those from Cheang and Zydney (2004), regarding the relatively low retention of α-lactalbumin by UF membranes; however, they do not align with other studies (Le Berre and Daufin 1998; Almécija *et al*. 2007). When subjecting milk to a single-stage MF (0.1 μm, i.e. a much larger pore size), Le Berre and Daufin (1998) retained ~36% of α-lactalbumin and β-lactoglobulin, and ~ 87% of bovine serum albumin (Table 4). Similarly, Almécija *et al*. (2007) reported a 67 and 81% retention of α-lactalbumin and β-lactoglobulin, respectively, when clarified whey was subjected to UF (300 kDa) with diafiltration, while retaining bovine serum albumin and immunoglobulin G at ~95%. Even after additional diafiltration, 46 and 70% of α-lactalbumin and β-lactoglobulin, respectively, were retained. The wide range of partition behaviours reported for whey proteins in the literature, particularly within the MF/UF category, makes interpretation of likely rejection coefficients a complex task. Membrane properties such as pore size (and distribution), module configuration and cascade arrangements, together with feed characteristics (including the ionic environments), and process conditions such as transmembrane pressure and fouling accumulation, all affect separation performance, and should be carefully considered during process design.

Fractionation of milk phospholipids

The isolation of milk phospholipids by membrane filtration is the focus of a number of studies seeking to exploit their nutraceutical and techno-functional properties (Huang *et al*. 2020). A summary of the operating parameters employed in these single-stage processes is presented in Table 3, and although many differences can be noted, the common trend is to seek process conditions conducive to counteract retention of casein micelles (50–600 nm diameter) (Fox and Brodkorb 2008) and protein aggregates that are similar in size to milk fat globule membranes fragments (300–1000 nm) (Holzmüller and Kulozik 2016).

When subjecting buttermilk whey, generated from renneting of rehydrated buttermilk powder, to MF (0.22 μm), Miocinovic *et al*. 2014 obtained a retentate with a phospholipid concentration of 20.97 g·100 g^{-1} of dry matter compared to 2.49 g·100 g^{-1} of dry matter in the starting material (Table 4). In comparison, when using buttermilk or butter serum, phospholipid concentration went from 3.18 and 9.32 g·100 g^{-1} of dry matter in the initial feed solutions to 8.05 and 23.31 g·100 g^{-1} of dry matter, respectively, in the corresponding retentate. This was associated with simultaneous casein retention, despite the higher concentration of milk fat globule membrane in the butter serum compared to buttermilk whey. These results are very similar to those obtained by Le *et al*. (2011) and Phan *et al*. (2013) who subjected reconstituted buttermilk to the same membrane cut-off (0.22 μm). The former authors obtained a phospholipid concentration of 8.4 g·100 g^{-1} of dry matter in the retentate compared to 3.36 g·100 g^{-1} in the starting material; the latter authors reported a phospholipid concentration of 9.30 g·100 g^{-1} of dry matter in the retentate compared to 3.27 g·100 g^{-1} of dry matter in the starting material. The slightly higher concentration factor obtained in these two studies compared to Miocinovic *et al*. 2014 is likely due to the addition of 1% trisodium citrate to the feed prior to MF in order to disrupt casein micelles, enhance permeation. More generally, the removal of casein is a crucial element in separation/concentration of MFGM components from a variety of dairy streams especially when considering commercial membrane processes which may be more susceptible to fouling during processing cycles, compared to flat-sheet membranes (Miocinovic *et al*. (2014)).

When subjecting buttermilk whey to 0.45 μm MF to retain larger fragments, Morin *et al*. (2006) reported a much lower enrichment factor for phospholipids, increasing from 1.31 g·100 g^{-1} of dry matter in the feed to 1.72 g·100 g^{-1} of dry matter in the retentate, likely due to the simultaneous

Table 3 Membrane processing conditions applied to milk phospholipid fractionation

Reference	Feed	Filtration process	VCF	TMP (MPa)	Temperature (°C)
Miocinovic *et al.* (2014)	Butter serum	MF (0.22 μm) using hydrophilised	2.5	–	45
	Buttermilk	polyvinylnilfluoride multi–flat-sheet membrane	2.5		
	Buttermilk whey		1.25		
Morin *et al.* (2006)	Buttermilk	MF (0.45 μm) using ceramic modules	2	0.08–0.095	8–10
	Buttermilk whey		–		–
Holzmüller and Kulozik (2016)	Buttermilk whey	MF (80 nm) using ceramic modules	–	0.1	50
Rombaut *et al.* (2007)	Acid buttermilk cheese whey	MF (0.1–0.45 μm) using cellulose acetate or polyethersulfone modules, UF (30 kDa) with polyethersulfone modules	4–5	0.1	40
Barry *et al.* (2017)	Buttermilk whey	UF (50 kDa) using spiral-wound polyethersulfone modules	11	–	50
Konrad *et al.* (2013)	Buttermilk whey	UF (30, 50, 100 and 300 kDa) using flat-sheet polyethersulfone modules	20	0.15–0.2	10–55
Hansen *et al.* (2020)	Raw whole milk	MF (1.4 μm) using tubular ceramic modules	–	0.05	50
Phan *et al.* (2013)	Buttermilk	MF (0.22 μm) using PVDF modules	2.25	0.035–0.055	45
Le *et al.* (2011)	Buttermilk	MF (0.22 μm) using PVDF modules	2.5	0.035–0.055	45

VCF, volume concentration factor; TMP, transmembrane pressure; MF, microfiltration; UF, ultrafiltration.

permeation of small fragments of MFGM (Table 4). Using UF (30 kDa) to minimise fat permeation, Rombaut *et al.* (2007) increased the concentration of phospholipids in acid buttermilk whey from 1.77 to 4.65 g·100 g^{-1} of dry matter in the retentate, whereby co-retention of whey proteins was observed. This enrichment was much lower than that obtained by Barry *et al.* (2017) when subjecting hydrolysed buttermilk whey to UF (50 kDa), whereby the lipid content was enriched to 60.07 g·100 g^{-1} dry matter in the retentate compared to 6.84 g·100 g^{-1} of dry matter in the initial feed. Extensive hydrolysis of the whey proteins prior to UF allowed permeation of low-molecular-weight peptides, which when coupled with diafiltration, increased lipid purity in the retentate. The use of higher filtration temperatures can also improve separation efficiency as reported by Konrad *et al.* (2013) for hydrolysed buttermilk whey. These authors observed a two-fold increase in phospholipid purity when increasing the filtration temperature from 10 to 40°C. These authors also observed increased phospholipid purity with increasing molecular weight cut-off from 6 to 8.5 g·100 g^{-1} of dry matter in the retentate when using 30 or 300 kDa membranes respectively. Rombaut *et al.* (2007) observed a lower MFGM retention using MF (0.10 or 0.15 μm) with phospholipid concentrations in the respective retentates of 1.90 and 2.23 g·100 g^{-1} of dry matter respectively; while for larger pore size (0.2–0.45 μm), no enrichment occurred due to permeation of MFGM fragments (Table 4). Conversely, when subjecting raw whole milk to MF (1.4 μm) thus through an even larger membrane cut-off, Hansen *et al.* (2020) obtained a retentate with a total polar lipid concentration of 7.1–7.2 g·100 g^{-1} of dry matter compared to 2.5 g·100 g^{-1} of dry matter in the initial milk, likely due to the feed having a milder processing history compared to acid buttermilk whey with preservation of large MFGM fragments. Considering the polydisperse nature of MFGM, a multistage MF process (0.1 to 10 μm) could be advantageous for separation of discrete fractions. However, the removal of casein and denatured whey proteins using an enzymatic or acidification step, or any other pre-treatment to partition colloidal or aggregated proteins is critical for selective concentration of MFGM components.

CONCLUSION

By taking advantage of the characteristics of each filtration step, the use of multistage membrane filtration processes enhances the efficiency of both concentration and fractionation processes for milk and derivatives thereof, compared to single-stage approaches. MF and UF processes can be used for the selective retention of fat, microorganisms and/or proteins from dairy streams and thereby improve the purity and yield of these fractions for use in tailored nutritional products. The resulting permeates can be concentrated by NF/RO processes with improved efficiency, relative to direct concentration of the feed material, due to their ability to achieve higher concentration factors due to lower osmotic pressure and viscosity. The permeates from NF/RO concentration processes can finally either be discharged to effluent treatment with a lower chemical oxygen demand than conventional dairy effluents or reused within commercial plants as boiler feed, cleaning-in-place or cooling waters. In general, outside of the research laboratory, membrane systems are

Table 4 Partition of feed components in studies focusing on the concentration or fractionation of dairy streams

Feed	Filtration process	% of feed components retained
Raw milk	MF (0.1 μm) (Le Berre and Daufin 1998)	23–42% of α-lactalbumin, 31–45% of β-lactoglobulin, 59–87% of bovine serum albumin, 70–72% of IgG, 49–99% of lactoferrin and 73–84% of lactoperoxidase
	MF (1.4 μm) (Hansen *et al*. 2020)	97.3–97.4% of fat globules, 3% of true proteins including 3% of caseins, 1–4% serum proteins and 20–24% total solids
Skim milk	MF (1.4 μm) (Blais *et al*. 2021)	100% of somatic cells and residual fat globules
	UF (6–8 kDa) (Atra *et al*. 2005)	87% of proteins
	Three-stage MF (0.1 μm) (Nelson and Barbano 2005)	>99% of fat globules, ~100% of caseins and 95% of serum proteins
	MF (0.1 μm) (Hartinger *et al*. 2019)	35% of α-lactalbumin, 30–95% of β-lactoglobulin and 70–95% of caseins
	MF (0.14 μm) (Heidebrecht *et al*. 2018)	35–55% of IgG and >99% of caseins
Whey	MF (0.2 μm) (Rektor and Vatai 2004)	99% of fat globules, 67% of proteins and 19% of lactose
	UF (100 kDa) (Rektor and Vatai 2004)	100% of fat globules; 75% of proteins and 40% of lactose
	UF (10 kDa) (Meyer and Kulozik 2016)	11% of dry matter, 100% of proteins, 9% of calcium and 3% of sodium
	UF (60 kDa) (Patil *et al*. 2014)	Varying levels of α-lactalbumin and β-lactoglobulin depending on pH and cascade configuration
	UF (6–8 kDa) (Atra *et al*. 2005)	83% of proteins
	UF (20 kDa) (Yorgun *et al*. 2008)	43% of chemical oxygen demand
	NF (<200 Da) (Yorgun *et al*. 2008)	58–97% of chemical oxygen demand
	NF/RO (<200 Da) (Yorgun *et al*. 2008)	94% of chemical oxygen demand
	RO (Yorgun *et al*. 2008)	90–92% of chemical oxygen demand
	UF (100 kDa) (Cheang and Zydney 2004)	0% of α-lactalbumin, 22% of β-lactoglobulin and >90% of bovine serum albumin
	UF (30 kDa) (Cheang and Zydney 2004)	10% of α-lactalbumin and ~100% of β-lactoglobulin
	UF (300 kDa) (Almécija *et al*. 2007)	43–100% of α-lactalbumin, 67–100% of β-lactoglobulin, 94–100% of bovine serum albumin, 53–100% of IgG and 26–100% of lactoferrin
MF permeate (from skim milk or cheese whey)	RO (Blais *et al*. 2021)	All feed components from MF permeate
	UF (10 kDa) (Britten and Pouliot 1996)	83–95% of nitrogen compounds and 16–18% of calcium
UF permeate (from skim milk or cheese whey)	NF (400 Da) (Atra *et al*. 2005)	100% of proteins and 96% of lactose
	UF (30 kDa) (Cheang and Zydney 2004)	5% of α-lactalbumin and 30% of β-lactoglobulin
	UF (100 kDa) (Cheang and Zydney 2004)	30% of β-lactoglobulin
Dairy wastewater	UF (5–30 kDa) (Luo *et al*. 2011)	99–100% of proteins, 100% of lipids and 0–34% of lactose
UF permeate (from dairy wastewater)	NF (90–400 Da) (Luo *et al*. 2011)	68–99% of lactose and 62–95% of salts
Buttermilk	MF (0.22 μm) (Miocinovic *et al*. 2014)	24% of total proteins, 31% of total lipids, 4% of ash, 2% of lactose and 31% of polar lipids
	MF (0.45 μm) (Morin *et al*. 2006)	>90% of lipids, 60–80% of proteins and 0–10% of ash
	MF (0.22 μm) (Phan *et al*. 2013)	90.3% of total proteins, 100% of total lipids, 20% of ash and 3% of lactose,
	MF (0.22 μm) (Le *et al*. 2011)	78% of total proteins, 97% of total lipids, 100% of phospholipids, 12% of ash and 6% of lactose
Buttermilk whey	MF (0.22 μm) (Miocinovic *et al*. 2014)	100% of total proteins, 100% of total lipids, 100% of ash, 5% of lactose and 100% of polar lipids

(continued)

Table 4 (Continued).

Feed	Filtration process	% of feed components retained
	MF (0.45 μm) (Morin *et al*. 2006)	>90% of lipids, 72–80% of proteins and 22–40% of ash
	MF (80 nm) (Holzmüller and Kulozik 2016)	35% of xanthine oxidase/dehydrogenase, 20% of BTN, butyrophilin and 70% of periodic acid Schiff protein
	MF (0.1–0.45 μm) (Rombaut *et al*. 2007)	7.4–45.8% of dry matter, 0.3–61% of ash, 29.3–75.9% of total proteins, 0.3–9.6% of reducing sugars, 54.2–96.4% lipids and 12.2–98.4% of polar lipids
	UF (30 kDa) (Rombaut *et al*. 2007)	37.9% of dry matter, 5.6% of ash, 29.3–82.5% of total proteins, 7.2% of reducing sugars, 99.9% lipids and 98.8% of polar lipids
	UF (50 kDa) (Barry *et al*. 2017)	80% of total lipids and 59% of phospholipids
	UF (30, 50, 100 and 300 kDa) (Konrad *et al*. 2013)	95–99% of phospholipids
Butter serum	MF (0.22 μm) (Miocinovic *et al*. 2014)	27% of total proteins, 31% of total lipids, 8% of ash, 0% of lactose and 34% of polar lipids

VCF, volume concentration factor; TMP, transmembrane pressure; MF, microfiltration; UF, ultrafiltration.

sequentially linked in terms of scale and complementary separation characteristics and it would be beneficial to see more multistage membrane approaches for concentration and isolation of dairy components described in the literature.

FUNDING

Herehau N Blais was funded under the Teagasc Walsh Scholarship.

ACKNOWLEDGEMENT

Open access funding provided by IReL.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Herehau N Blais: Writing – original draft. **Karin Schroën:** Writing – review and editing. **John T Tobin:** Writing – review and editing.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated, or the article describes entirely theoretical research.

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