[0005] Accordingly, it would be desirable to develop a method of filtering a purified vWF mixture in a manner that does not substantially damage the vWF proteins, yet which method still permits a suitably high process throughput (i.e., filtration rate) over time. Additionally, it would be desirable to develop a filtering method generally applicable to any protein, such that the general protein can be filtered (e.g., sterile filtered) at an efficient rate without incurring substantial damage to/loss of the protein.

SUMMARY

[0006] The disclosed method is useful for filtering a protein in a liquid mixture in either a batch or continuous manner that does not substantially damage or otherwise limit the recovery of the protein in the filtration filtrate. The method generally applies a counter pressure to the filtrate to accurately reduce and control the pressure differential across a filter. The disclosed method has the advantage that relatively high filtration flow rates can be achieved at relatively low pressure differentials, in contrast to high pressure differentials which actually reduce the filtration flow rate of protein liquid mixtures. Further, the method can recover substantially all of the protein that is initially present in the liquid mixture.

[0007] More specifically, the disclosure provides a method of filtering a liquid protein mixture. According to one embodiment, the method includes providing a liquid mixture at a first pressure P_1 and passing the liquid mixture through a filter to form a filtrate at a second pressure P_2, and applying a counter pressure to the filtrate such that a pressure differential $P_1 - P_2$ is not more than about 300 mbar. In another embodiment, the method includes the steps of providing a liquid mixture at a first pressure P_1, and passing the liquid mixture through a filter to form a filtrate at a second pressure P_2, and applying a counter pressure to the filtrate sufficient to yield an average flow rate of the filtrate of at least about 300 g/min.m^2 of filter surface area. The liquid mixture includes a carrier liquid, a protein at a first concentration C_1 relative to the carrier liquid, and a dispersed contaminant. The filtrate includes the carrier liquid and the protein at a second concentration C_2 relative to the carrier liquid. The filter is sized to remove at least a portion of the dispersed contaminant from the liquid mixture.

[007a] In one aspect, there is provided a method of filtering a liquid protein mixture, the method comprising:

providing a liquid mixture at a first pressure (P_1), the liquid mixture comprising a carrier liquid, a protein at a first concentration (C_1) relative to the carrier liquid, and a dispersed contaminant;

passing the liquid mixture through a filter to form a filtrate at a second pressure (P_2), the filtrate comprising the carrier liquid and the protein at a second concentration (C_2) relative to the carrier liquid, wherein the filter is sized to remove at least a portion of the dispersed contaminant from the liquid mixture; and

applying a counter pressure to the filtrate to ensure that a pressure differential between the first and second pressures ($P_1 - P_2$) is: (a) not more than about 300 mbar; and/or (b) sufficient to yield an average filtrate flow of at least 300 g/ min·m^2 of filter surface area,

wherein the protein comprises a shear-sensitive protein.

[0008] In yet another embodiment, the method is capable of filtering an aqueous protein mixture, and includes the steps of providing an aqueous mixture at a first pressure P_1, passing the aqueous mixture through a porous membrane filter to form a filtrate at a second pressure P_2, and applying a counter pressure to the filtrate such that a pressure differential $P_1 - P_2$ is not more than about 90 mbar. The aqueous mixture includes water and vWF at a first

concentration C_1 relative to the water. The filtrate includes water and the vWF at a second concentration C_2 relative to the water. The porous membrane filter includes pores sized from about 0.1 μm to about 0.5 μm.

[0008a] In another aspect, there is provided a method of filtering an aqueous protein mixture, the method comprising:

providing an aqueous mixture at a first pressure (P_1), the aqueous mixture comprising water and von Willebrand factor (vWF) at a first concentration (C_1) relative to the water;

passing the aqueous mixture through a porous membrane filter to form a filtrate at a second pressure (P_2), the filtrate comprising the water and the vWF at a second concentration (C_2) relative to the water, wherein the porous membrane filter comprises pores sized from about 0.1 μm to about 0.5 μm; and

applying a counter pressure to the filtrate to ensure that a pressure differential between the first and second pressures ($P_1 - P_2$) is not more than about 90 mbar.

[0009] In any of the above embodiments, the protein is preferably a shear-sensitive protein and/or a blood coagulation cascade protein. Further, the protein is preferably recovered in the filtrate such that a recovery ratio C_2/C_1 is at least about 0.95, more preferably at least about 0.99. Additionally, the pressure differential $P_1 - P_2$ is preferably not more than about 90 mbar and the first pressure P_1 is preferably at least about 200 mbar gauge. Preferred embodiments of the above methods include those in which the carrier liquid is water, and/or the dispersed contaminant includes microorganisms. The protein can include von Willebrand Factor, Factor VIII, Factor XIII, and mixtures thereof. The filter preferably includes a porous membrane filter having pores sized from about 0.1 μm to about 0.5 μm, more preferably sized at about 0.2 μm or about 0.22 μm. Preferably, the filtrate product is substantially free of the dispersed contaminant.

[0010] Filtration of a protein under the application of counter-pressure allows the recovery the protein at high relative concentrations, high relative filtrate flow rates, and substantially constant filtrate flow rates that are not otherwise attainable in the absence of counter-pressure. This is in contrast to the general application of filter theory at least with respect to the filtrate flow rate, which predicts that the filtrate flow rate increases with increasing pressure differential across the filter (i.e., in the absence of counter-pressure).

[0011] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawing. While the compositions, films, and packets described herein are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the disclosure to the specific embodiments described herein.

BRIEF DESCRIPTION OF THE DRAWING

[0012] Two drawing figures are appended hereto to facilitate the understanding of the disclosure.

[0013] Figure 1 is a cross-sectional view of an axisymmetric cartridge filter for use in the counter-pressure filtration of proteins.

CLAIMS

1. A method of filtering a liquid protein mixture, the method comprising:

providing a liquid mixture at a first pressure (P_1), the liquid mixture comprising a carrier liquid, a protein at a first concentration (C_1) relative to the carrier liquid and a dispersed contaminant;

passing the liquid mixture through a filter to form a filtrate at a second pressure (P_2), the filtrate comprising the carrier liquid and the protein at a second concentration (C_2) relative to the carrier liquid, wherein the filter is sized to remove at least a portion of the dispersed contaminant from the liquid mixture; and

applying a counter pressure to the filtrate to ensure that a pressure differential between the first and second pressures ($P_1 - P_2$) is: (a) not more than about 300 mbar; and/or (b) sufficient to yield an average filtrate flow of at least 300 g/min•m^2 of filter surface area,

wherein the protein comprises a shear-sensitive protein.

2. The method of claim 1, wherein the pressure differential between the first and second pressures ($P_1 - P_2$) is not more than about 90 mbar.

3. The method of claim 1 or claim 2, wherein the protein comprises a blood coagulation cascade protein.

4. The method of any one of claims 1 to 3, wherein at least about 95% of the protein present in the liquid mixture is recovered in the filtrate.

5. The method of any one of claims 1 to 4, wherein at least about 99% of the protein present in the liquid mixture is recovered in the filtrate.

6. The method of any one of claims 1 to 5, wherein the first pressure (P_1) is at least about 200 mbar gauge.

7. The method of any one of claims 1 to 6, wherein the carrier liquid comprises water.

8. The method of any one of claims 1 to 7, wherein the protein is selected from the group consisting of von Willebrand factor (vWF), Factor VIII, Factor XIII and mixtures thereof.

9. The method of any one of claims 1 to 8, wherein the dispersed contaminant comprises a microorganism.

10. The method of any one of claims 1 to 9, wherein the filtrate is substantially free of the dispersed contaminant.

11. The method of any one of claims 1 to 10, wherein the filter comprises a porous membrane, the porous membrane comprising pores sized from about 0.1 μm to about 0.5 μm.

12. The method of claim 11, wherein the pores are sized at about 0.2 μm or about 0.22 μm.

13. A method of filtering an aqueous protein mixture, the method comprising:

providing an aqueous mixture at a first pressure (P_1), the aqueous mixture comprising water and von Willebrand factor (vWF) at a first concentration (C_1) relative to the water;

passing the aqueous mixture through a porous membrane filter to form a filtrate at a second pressure (P_2), the filtrate comprising the water and the vWF at a second concentration (C_2) relative to the water, wherein the porous membrane filter comprises pores sized from about 0.1 μm to about 0.5 μm; and

applying a counter pressure to the filtrate to ensure that a pressure differential between the first and second pressures ($P_1 - P_2$) is not more than about 90 mbar.

14. The method of claim 13, wherein at least about 95% of the vWF present in the liquid mixture is recovered in the filtrate.

15. The method of claim 13 or claim 14, wherein at least about 99% of the vWF present in the liquid mixture is recovered in the filtrate.

16. The method of any one of claims 13 to 15, wherein the pores are sized at about 0.2 μm or about 0.22 μm.

17. The method of any one of claims 13 to 16, wherein the aqueous mixture further comprises a microorganism population, at least a portion of the population of which is removed from the aqueous mixture by the porous membrane filter.

18. The method of any one of claims 13 to 17, wherein the P_1 is at least about 200 mbar gauge.