

[NPL 9] Turker M, Hubble J. Membrane fouling in a constant-flux ultrafiltration cell, J. Membr. Sci. 34 (1987) 267.

[NPL 10] Van Reis R, Zydney A. Membrane separations in biotechnology. Curr Opin Biotechnol (2001), 12:208-211.

[Summary of Invention]

[0008]

The industry standard technology for concentrating proteins at manufacturing scale is ultrafiltration by tangential flow. Key challenges for products with high final concentrations are to prevent membrane fouling and to overcome high feed pressure.

[0009]

In general terms, the present disclosure describes the specific manipulation of process parameters for successful concentration of proteins, such as an antibody preparation, pharmaceutical formulations containing such a preparation, and their use in human therapy or animal therapy.

[0010]

In embodiments the present disclosure provides a method wherein a feed flow rate is maintained at a high flow rate until an optimal protein concentration then reduced to a lower value to continue further concentrating. For example, concentration is performed at a feed flow rate equal or greater than 200 LMH until the retentate solution is concentrated to a protein concentration greater than 200 g/L, where a feed pressure builds up to 85-100% of the specified maximum feed pressure of an ultrafiltration membrane, then further concentration is continued at a feed flow rate equal or less than 120 LMH. The attainable protein concentration within the operational limits is higher than the conventional process comprising either one step with a constant feed flow rate or two steps with a step-down feed flow control on early transition.

[0011]

The present disclosure also provides, in embodiments, a more preferable method wherein a feed flow rate is maintained as high as possible until the end of the concentration process. For example, a feed flow rate is automatically controlled in a manner to maintain a feed pressure within 85-100% of the specified maximum feed pressure of an ultrafiltration membrane once a feed pressure reaches 85-100% of the specified maximum feed pressure of an ultrafiltration membrane under a constant feed flow rate.

[0012]

The present disclosure also provides, in embodiments, the effectiveness of a circulation step inserted in the middle of a concentration process. For example, 20 minutes circulation at a feed flow rate of 10-80 LMH is inserted once a feed pressure reaches 85-100% of the specified maximum feed pressure of an ultrafiltration membrane under a constant feed flow rate. This circulation step can mitigate the feed pressure buildup during a subsequent ultrafiltration process.

[0012a] In one aspect, there is provided a method of producing a pharmaceutical liquid composition comprising an antibody, wherein the method comprises steps as below:

(a) preparing highly concentrated antibody solution by a method for preparing a composition comprising highly concentrated antibodies by ultrafiltration, wherein the method comprises the steps of:

1) regulating the feed flow rate to allow the value of feed pressure applied to an ultrafiltration membrane to increase to 85-100% of a specified maximum feed pressure of an ultrafiltration membrane; and

2) decreasing the feed flow rate to maintain or decrease the value of the feed pressure applied to the ultrafiltration membrane after the step (1); and

(b) preparing a pharmaceutical liquid composition comprising an antibody by adding a pharmaceutically acceptable carrier into the above concentrated antibody solution.

[0013]

In summary, it is an object of the present ~~invention~~disclosure to provide the following [1] to [33].

cut off of 30 kDa or less.

[34] The method of [1], wherein the composition comprises highly concentrated anti-human interleukin-6 receptor monoclonal antibodies.

[35] The method of [34], wherein the composition comprises highly concentrated tocilizumab.

[36] A liquid composition which comprises highly concentrated antibodies prepared by the method of [1].

[37] A pharmaceutical liquid composition which comprises highly concentrated antibodies prepared by the method of [1] and a pharmaceutically acceptable carrier.

[38] A method for preparing a composition comprising highly concentrated proteins by ultrafiltration, wherein the method comprises the steps of:

1) regulating a feed flow rate to allow the value of feed pressure applied to an ultrafiltration membrane to increase to 85-100% of a specified maximum feed pressure of an ultrafiltration membrane; and

2) decreasing the feed flow rate to maintain or decrease the value of the feed pressure applied to the ultrafiltration membrane after the step (1).

[0014]

It will also be understood that both the foregoing summary of the present ~~invention~~disclosure and the following detailed description are of exemplified embodiments, and not restrictive of the present ~~invention~~disclosure or other alternate embodiments of the present ~~invention~~disclosure. Other objects and features of the ~~invention~~disclosure will become more fully apparent when the following detailed description is read in conjunction with the accompanying figures and examples. In particular, while the ~~invention~~disclosure is described herein with reference to a number of specific embodiments, it will be appreciated that the description is illustrative of the ~~invention~~disclosure and is not constructed as limiting of the ~~invention~~disclosure. Various modifications and applications may occur to those who are skilled in the art, without departing from the spirit and the scope of the ~~invention~~disclosure, as described by the appended claims. Likewise, other objects, features, benefits and advantages of the present ~~invention~~disclosure will be apparent from this summary and certain embodiments described below, and will be readily apparent to those skilled in the art. Such objects, features, benefits and advantages will be apparent from the above in conjunction with the accompanying examples, data, figures and all reasonable inferences to be drawn therefrom, alone or with consideration of the references incorporated herein.

[Brief Description of Drawings]

[0015]

Various aspects and applications of the present invention will become apparent to the skilled artisan upon consideration of the brief description of the figures and the detailed description of the present invention and its preferred embodiments that follows:

Claims

[Claim 1]

A method of producing a pharmaceutical liquid composition comprising an antibody, wherein the method comprises steps as below:

(a) preparing highly concentrated antibody solution by a method for preparing a composition comprising highly concentrated antibodies by ultrafiltration, wherein the method comprises the steps of:

1) regulating the feed flow rate to allow the value of feed pressure applied to an ultrafiltration membrane to increase to 85-100% of a specified maximum feed pressure of an ultrafiltration membrane; and
2) decreasing the feed flow rate to maintain or decrease the value of the feed pressure applied to the ultrafiltration membrane after the step (1); and

(b) preparing a pharmaceutical liquid composition comprising an antibody by adding a pharmaceutically acceptable carrier into the above concentrated antibody solution.

[Claim 2]

The method of claim 1, wherein the antibody preparation is processed at ambient temperature.

[Claim 3]

The method of claim 1, wherein the antibody preparation is processed at a temperature from 10 to 30 degrees C.

[Claim 4]

The method of claim 1, wherein the antibody preparation is processed at a temperature from 15 to 30 degrees C.

[Claim 5]

The method of claim 1, wherein the highly concentrated antibodies have a high concentration of above 100 g/L or a viscosity above 2 mPa.s.

[Claim 6]

The method of claim 1, wherein the highly concentrated antibodies have a high concentration of above 200 g/L or a viscosity above 10 mPa.s.

[Claim 7]

The method of claim 1, wherein the highly concentrated antibodies have a high concentration of above 250 g/L or a viscosity above 40 mPa.s.

[Claim 8]

The method of claim 1, wherein the feed flow rate in step (1) is maintained at 200 LMH ($\text{L}/\text{m}^2/\text{hour}$) or higher.

[Claim 9]

The method of claim 1, wherein the feed flow rate in step (1) is maintained at 250 LMH ($\text{L}/\text{m}^2/\text{hour}$) or higher.

[Claim 10]

The method of claim 1, 8 and 9, wherein the feed flow rate in step (1) is maintained at a constant rate.

[Claim 11]

The method of claim 1, wherein the maximum value of the feed pressure applied to an ultrafiltration membrane in step (1) is from 2.0 bar to 4.0 bar.

[Claim 12]

The method of claim 1, wherein the maximum value of the feed pressure applied to an ultrafiltration membrane in step (1) is 3.5 bar.

[Claim 13]

The method of claim 1, wherein the maximum value of the feed pressure applied to an ultrafiltration membrane in step (1) is 85-100% of the specified maximum feed pressure of the ultrafiltration membrane.

[Claim 14]

The method of claim 1, wherein step (1) is transitioned to step (2) when the retentate solution is concentrated to a protein concentration greater than 200 g/L.

[Claim 15]

The method of claim 1, wherein step (1) is transitioned to step (2) when the retentate solution is concentrated to a protein concentration equal or greater than 220 g/L.

[Claim 16]

The method of claim 1, wherein step (1) is transitioned to step (2) when the retentate solution is concentrated to a protein concentration equal to 240 g/L.

[Claim 17]

The method of claim 13, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at a constant rate.

[Claim 18]

The method of claim 13 or 17, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at 120 LMH ($\text{L}/\text{m}^2/\text{hour}$) or lower.

[Claim 19]

The method of claim 13 or 17, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at 80 LMH ($\text{L}/\text{m}^2/\text{hour}$) or lower.

[Claim 20]

The method of claim 1, wherein the value of the feed pressure applied to an ultrafiltration membrane in step (2) is maintained at a constant value.

[Claim 21]

The method of claim 1, wherein the value of the feed pressure applied to an ultrafiltration membrane in step (2) is maintained within 85-100% of the specified maximum feed pressure of the ultrafiltration membrane by reducing the feed flow rate.

[Claim 22]

The method of claim 20 or 21, wherein the feed flow rate is automatically regulated in a manner to maintain the feed pressure within 85-100% of the specified maximum feed pressure of the ultrafiltration membrane by a feedback control between a feed pressure and a feed flow rate.

[Claim 23]

The method of claim 1, further comprising between step (1) and step (2), the following step of: 3) recirculating the antibody preparation through the membrane with a permeate valve closed.

[Claim 24]

The method of claim 23, wherein the antibody preparation is recirculated with a retentate pressure control valve fully open.

[Claim 25]

The method of claim 23, wherein the feed flow rate in step (3) is maintained at a constant flow rate between 5 to 120 LMH ($\text{L}/\text{m}^2/\text{hour}$).

[Claim 26]

The method of claim 23, wherein the feed flow rate in step (3) is maintained at a constant flow rate between 10 to 80 LMH (L/m²/hour).

[Claim 27]

The method of claim 1, wherein the buffer composition of the antibody preparation is between 10 to 30 mmol/L histidine.

[Claim 28]

The method of claim 1, wherein the buffer composition of the antibody preparation is 20 mmol/L histidine.

[Claim 29]

The method of claim 1, wherein the pH of the antibody preparation is between pH 3.0 and pH 10.0.

[Claim 30]

The method of claim 1, wherein the pH of the antibody preparation is between pH 5.5 and pH 6.5.

[Claim 31]

The method of claim 1, wherein the pH of the antibody preparation is pH 6.0.

[Claim 32]

The method of claim 1, wherein the ultrafiltration membrane has a molecular weight cut off of 50 kDa or less.

[Claim 33]

The method of claim 1, wherein the ultrafiltration membrane has a molecular weight cut off of 30 kDa or less.

[Claim 34]

The method of claim 1, wherein the composition comprises highly concentrated anti-human interleukin-6 receptor monoclonal antibodies.

[Claim 35]

The method of claim 34, wherein the composition comprises highly concentrated tocilizumab.

Claims

- [Claim 1] A method for preparing a composition comprising highly concentrated antibodies by ultrafiltration, wherein the method comprises the steps of:
1) regulating the feed flow rate to allow the value of feed pressure applied to an ultrafiltration membrane to increase to 85-100% of a specified maximum feed pressure of an ultrafiltration membrane; and
2) decreasing the feed flow rate to maintain or decrease the value of the feed pressure applied to the ultrafiltration membrane after the step (1).
- [Claim 2] The method of claim 1, wherein the antibody preparation is processed at ambient temperature.
- [Claim 3] The method of claim 1, wherein the antibody preparation is processed at a temperature from 10 to 30 degrees C.
- [Claim 4] The method of claim 1, wherein the antibody preparation is processed at a temperature from 15 to 30 degrees C.
- [Claim 5] The method of claim 1, wherein the highly concentrated antibodies have a high concentration of above 100 g/L or a viscosity above 2 mPa.s.
- [Claim 6] The method of claim 1, wherein the highly concentrated antibodies have a high concentration of above 200 g/L or a viscosity above 10 mPa.s.
- [Claim 7] The method of claim 1, wherein the highly concentrated antibodies have a high concentration of above 250 g/L or a viscosity above 40 mPa.s.
- [Claim 8] The method of claim 1, wherein the feed flow rate in step (1) is maintained at 200 LMH (L/m²/hour) or higher.
- [Claim 9] The method of claim 1, wherein the feed flow rate in step (1) is maintained at 250 LMH (L/m²/hour) or higher.
- [Claim 10] The method of claim 1, 8 and 9, wherein the feed flow rate in step (1) is maintained at a constant rate.
- [Claim 11] The method of claim 1, wherein the maximum value of the feed pressure applied to an ultrafiltration membrane in step (1) is from 2.0 bar to 4.0 bar.
- [Claim 12] The method of claim 1, wherein the maximum value of the feed pressure applied to an ultrafiltration membrane in step (1) is 3.5 bar.
- [Claim 13] The method of claim 1, wherein the maximum value of the feed pressure applied to an ultrafiltration membrane in step (1) is 85-100% of the specified maximum feed pressure of the ultrafiltration

membrane.

[Claim 14] The method of claim 1, wherein step (1) is transitioned to step (2) when the retentate solution is concentrated to a protein concentration greater than 200 g/L.

[Claim 15] The method of claim 1, wherein step (1) is transitioned to step (2) when the retentate solution is concentrated to a protein concentration equal or greater than 220 g/L.

[Claim 16] The method of claim 1, wherein step (1) is transitioned to step (2) when the retentate solution is concentrated to a protein concentration equal to 240 g/L.

[Claim 17] The method of claim 13, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at a constant rate.

[Claim 18] The method of claim 13 or 17, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at 120 LMH (L/m²/hour) or lower.

[Claim 19] The method of claim 13 or 17, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at 80 LMH (L/m²/hour) or lower.

[Claim 20] The method of claim 1, wherein the value of the feed pressure applied to an ultrafiltration membrane in step (2) is maintained at a constant value.

[Claim 21] The method of claim 1, wherein the value of the feed pressure applied to an ultrafiltration membrane in step (2) is maintained within 85-100% of the specified maximum feed pressure of the ultrafiltration membrane by reducing the feed flow rate.

[Claim 22] The method of claim 20 or 21, wherein the feed flow rate is automatically regulated in a manner to maintain the feed pressure within 85-100% of the specified maximum feed pressure of the ultrafiltration membrane by a feedback control between a feed pressure and a feed flow rate.

[Claim 23] The method of claim 1, further comprising between step (1) and step (2), the following step of:
3) recirculating the antibody preparation through the membrane with a permeate valve closed.

[Claim 24] The method of claim 23, wherein the antibody preparation is recirculated with a retentate pressure control valve fully open.

[Claim 25] The method of claim 23, wherein the feed flow rate in step (3) is

- maintained at a constant flow rate between 5 to 120 LMH (L/m²/hour).
- [Claim 26] The method of claim 23, wherein the feed flow rate in step (3) is maintained at a constant flow rate between 10 to 80 LMH (L/m²/hour).
- [Claim 27] The method of claim 1, wherein the buffer composition of the antibody preparation is between 10 to 30 mmol/L histidine.
- [Claim 28] The method of claim 1, wherein the buffer composition of the antibody preparation is 20 mmol/L histidine.
- [Claim 29] The method of claim 1, wherein the pH of the antibody preparation is between pH 3.0 and pH 10.0.
- [Claim 30] The method of claim 1, wherein the pH of the antibody preparation is between pH 5.5 and pH 6.5.
- [Claim 31] The method of claim 1, wherein the pH of the antibody preparation is pH 6.0.
- [Claim 32] The method of claim 1, wherein the ultrafiltration membrane has a molecular weight cut off of 50 kDa or less.
- [Claim 33] The method of claim 1, wherein the ultrafiltration membrane has a molecular weight cut off of 30 kDa or less.
- [Claim 34] The method of claim 1, wherein the composition comprises highly concentrated anti-human interleukin-6 receptor monoclonal antibodies.
- [Claim 35] The method of claim 34, wherein the composition comprises highly concentrated tocilizumab.
- [Claim 36] A liquid composition which comprises highly concentrated antibodies prepared by the method of claim 1.
- [Claim 37] A pharmaceutical liquid composition which comprises highly concentrated antibodies prepared by the method of claim 1 and a pharmaceutically acceptable carrier.
- [Claim 38] A method for preparing a composition comprising highly concentrated proteins by ultrafiltration, wherein the method comprises the steps of:
1) regulating the feed flow rate to allow the value of feed pressure applied to an ultrafiltration membrane to increase to 85-100% of a specified maximum feed pressure of an ultrafiltration membrane; and
2) decreasing the feed flow rate to maintain or decrease the value of the feed pressure applied to the ultrafiltration membrane after the step (1).