Claims

[Claim 1]
A method of producing a pharmaceutical liquid composition comprising an antibody, wherein the method comprises steps as below:
(a) preparing antibody solution by a method for preparing a composition comprising antibodies concentrated to a protein concentration greater than 200 g/L by ultrafiltration, wherein the method comprises the steps of:

1) maintaining 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, wherein the maximum value of the feed pressure is from 2.0 bar to 4.0 bar;
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
3) circulating with a permeate side closed under a constant retentate flow rate and then being recovered; and

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

[Claim 2]
The method of claim 1, wherein the preparing step (a) is processed at ambient temperature.

[Claim 3]
The method of claim 1, wherein the preparing step (a) is processed at a temperature from 10 to 30 degrees C.

[Claim 4]
The method of claim 1, wherein the preparing step (a) is processed at a temperature from 15 to 30 degrees C.

[Claim 5]
The method of claim 1, wherein the antibody solution has a high concentration of above 100 g/L or a viscosity above 2 mPa.s.

[Claim 6]
The method of claim 1, wherein the antibody solution has a high concentration of above 200 g/L or a viscosity above 10 mPa.s.

[Claim 7]

The method of claim 1, wherein the antibody solution has 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/m^2/hour) or higher.

[Claim 9]
The method of claim 1, wherein the feed flow rate in step (1) is maintained at 250 LMH (L/m^2/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 3.5 bar.

[Claim 12]
The method of claim 1, wherein step (1) is transitioned to step (2) when a retentate solution is concentrated to a protein concentration greater than 200 g/L.

[Claim 13]
The method of claim 1, wherein step (1) is transitioned to step (2) when a retentate solution is concentrated to a protein concentration equal or greater than 220 g/L.

[Claim 14]
The method of claim 1, wherein step (1) is transitioned to step (2) when a retentate solution is concentrated to a protein concentration equal to 240 g/L.

[Claim 15]
The method of claim 1, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at a constant rate.

[Claim 16]
The method of claim 1 or 15, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at 120 LMH (L/m^2/hour) or lower.

[Claim 17]
The method of claim 1 or 15, wherein the feed flow rate after the value of the feed pressure is decreased in step (2) is maintained at 80 LMH (L/m^2/hour) or lower.

[Claim 18]
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 19]
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 20]
The method of claim 18 or 19, 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 21]
The method of claim 1, further comprising between step (1) and step (2), the following step of:
4) recirculating the antibody preparation processed by step (1) through the membrane with a permeate valve closed.

[Claim 22]
The method of claim 21, wherein the recirculating step is performed with a retentate pressure control valve fully open.

[Claim 23]
The method of claim 21, wherein the feed flow rate in step (4) is maintained at a constant flow rate between 5 to 120 LMH (L/m^2/hour).

[Claim 24]
The method of claim 21, wherein the feed flow rate in step (4) is maintained at a constant flow rate between 10 to 80 LMH (L/m^2/hour).

[Claim 25]

The method of claim 1, wherein a buffer composition of the antibody solution prepared by step (a) is between 10 to 30 mmol/L histidine.

[Claim 26]
The method of claim 1, wherein a buffer composition of the antibody solution prepared by step (a) is 20 mmol/L histidine.

[Claim 27]
The method of claim 1, wherein the pH of the antibody solution prepared by step (a) is between pH 3.0 and pH 10.0.

[Claim 28]
The method of claim 1, wherein the pH of the antibody solution prepared by step (a) is between pH 5.5 and pH 6.5.

[Claim 29]
The method of claim 1, wherein the pH of the antibody solution prepared by step (a) is pH 6.0.

[Claim 30]
The method of claim 1, wherein the ultrafiltration membrane has a molecular weight cut off of 50 kDa or less.

[Claim 31]
The method of claim 1, wherein the ultrafiltration membrane has a molecular weight cut off of 30 kDa or less.

[Claim 32]
The method of claim 1, wherein the composition comprises anti-human interleukin-6 receptor monoclonal antibodies.

[Claim 33]
The method of claim 32, wherein the composition comprises tocilizumab.

[Claim 34]
A method for preparing a composition comprising proteins concentrated by ultrafiltration,

wherein the method comprises concentrating a protein preparation by ultrafiltration of the preparation, said ultrafiltration comprising:

a) maintaining a feed flow rate of the preparation to allow a value of feed pressure applied to an ultrafiltration membrane to increase to a value from 2.0 bar to 4.0 bar;

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

c) circulating with a permeate valve closed under a constant retentate flow rate and then being recovered,

wherein the protein preparation directly after said ultrafiltration has a protein concentration above 200 g/L or a viscosity above 10 mPa·s.

[Claim 35]

A method for preparing a composition comprising proteins concentrated by ultrafiltration, wherein the method comprises concentrating a protein preparation by ultrafiltration of the preparation, said ultrafiltration comprising:

a) maintaining a feed flow rate of the preparation to allow a value of feed pressure applied to an ultrafiltration membrane to increase to a value from 3.5 bar to 4.0 bar;

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

c) circulating with a permeate valve closed under a constant retentate flow rate and then being recovered,

wherein the protein preparation directly after said ultrafiltration has a protein concentration above 200 g/L or a viscosity above 10 mPa·s.

[Claim 36]

The method of claim 34, wherein the protein is an antibody.

[Claim 37]

The method of claim 35, wherein the protein is an antibody.