BRIEF SUMMARY ~~OF THE INVENTION~~

[0008] In one embodiment~~aspect~~, the present disclosure~~invention~~ provides an aqueous composition comprising more than about 180 grams of protein per liter of the composition, and at least 95% of the protein is IgG, such as human IgG. In some embodiments, the composition is produced by a process leading to a product suitable for subcutaneous and intravenous administration, and can be treated at elevated temperature in the final container to inactivate viruses regardless which concentration is adjusted between a concentration range of 10 to 22% of protein. In some cases, the protein concentration in the composition is at or about 20% (w/v). In other cases, the composition may further comprise about 0.1-0.3 M glycine. The composition of this invention may have varying pH, such as about 3-6, or about 4-6.

[0009] In another embodiment~~aspect~~, this disclosure~~invention~~ provides a method for preparing a composition of concentrated IgG from plasma with the improvement comprising the steps of: (1) concentrating protein in a plasma preparation to at or about 5% (w/v) by ultrafiltration; and (2) further concentrating the protein in the preparation to at or about 20% (w/v) by diafiltration. At least 95% of the protein referred to in the composition is IgG, such as human IgG. In some embodiments, step (1) is performed using an ultrafiltration membrane with a nominal molecular weight cut off (NMWCO) of 100 kDa or less. In other embodiments, step (2) is performed against a diafiltration buffer of glycine with a pH of 4.2 ± 0.1. The diafiltration buffer in some cases has 0.25 M glycine and a pH of 4.0. In some particular embodiments, the protein concentration after step (2) is higher than 20% (w/v) and is subsequently adjusted to at or about 20% (w/v) with a diafiltration buffer.

[0010] In another embodiment~~aspect~~, the disclosure~~invention~~ provides a method for preparing a composition of concentrated IgG from plasma, comprising the steps of:

(1) separating liquid and precipitate from plasma by centrifugation;
(2) mixing pre-cooled ethanol with the liquid from (1) to form a mixture, which has an ethanol concentration of at or about 8% (v/v);
(3) separating liquid and precipitate from the mixture of (2) by centrifugation;
(4) adjusting pH and ethanol concentration of the liquid from (3) to at or about 7.0 and 20-25% (v/v), respectively, thereby forming a mixture;
(5) separating liquid and precipitate from the mixture of (4) by centrifugation;

and eluted with a buffer of 35 mM monobasic sodium phosphate, 10 mM Tris, pH 8.5 ± 0.1, conductivity 5.0 ± 0.2 mS/cm. In some embodiments, the eluate from step (10) is adjusted to a pH of 6.4 ± 0.2 and conductivity of about 1.5 to 2.5 mS/cm prior to step (11). In some embodiments, the effluent of step (11) is passed through a filter of 0.2 μm or smaller pore size prior to step (12). In some embodiments, the ultrafiltrate of step (13) has a protein concentration of at or about 5 ± 1% (w/v). In other embodiments, the ultrafiltration membrane of step (13) has a nominal molecular weight cut off (NMWCO) of 50 kDa or less. In some embodiments, the diafiltration buffer of step (14) is a 0.25 M glycine solution with a pH of 4.2 ± 0.1. In other embodiments, the solution from step (14) has a protein concentration greater than 20% (w/v) and is subsequently adjusted to at or about 20.4 ± 0.4% (w/v) with the diafiltration buffer. In some embodiments, steps (13) and (14) are performed at a temperature of about 2 to 8°C. In other embodiments, the preparation method further comprises a step of dispensing the sterilized solution of step (15) into containers under sterile conditions before the containers are sealed.

[0012] In other embodiments, the method described above may further comprise a step of storing the sealed containers at about 30 to 32°C for about 21 to 22 days; or the method may further comprise a formulation step to render the 20% IgG product as stable as the 10% state of the art intravenous formulation.

[0013] In yet another embodimentaspect, this disclosureinvention provides an aqueous composition that is produced by the preparation method described above and comprises at least 18% (w/v) immunoglobulin, for instance, at least 20% (w/v) immunoglobulin.

[0014] In a further embodimentaspect, the present disclosureinvention provides a method for treating a patient suffering from an immunodeficiency, an autoimmune disease, or an acute infection, comprising administering to the patient an effective amount of the composition as described above.

[0014a] In one aspect, there is provided a method for preparing a composition of concentrated IgG from plasma, the method comprising the steps of:

(A) concentrating a nanofiltrate comprising IgG by using a first ultra-/diafiltration system comprising a first ultra-/diafiltration membrane, thereby forming a first concentrate;

(B) diafiltration of the first concentrate using the first ultra-/diafiltration system, thereby forming a solution;

(C) concentrating the solution to a bulk solution having a protein concentration of greater than 20% (w/v) using the first ultra-/diafiltration system;

(D) collecting the bulk solution from the first ultra-/diafiltration system;

(E) post-washing the first ultra-/diafiltration system by re-circulating a post-wash buffer through the first ultra-/diafiltration system, wherein the first ultra-/diafiltration system is washed with a volume of post-wash buffer of at least two times the dead volume of the first ultra-/diafiltration system, thereby forming a first IgG post-wash solution;

(F) transferring the first IgG post-wash solution from the first ultra-/diafiltration system into a second ultra-/diafiltration system comprising a second ultra-/diafiltration membrane of the same type as the first ultra-/diafiltration membrane, wherein the second ultra-/diafiltration system is smaller than the first ultra-/diafiltration system;

(G) concentrating the first IgG post-wash solution to a protein concentration of greater than 20% (w/v) using the second ultra-/diafiltration system, thereby forming a first post-wash concentrate; and

(H) combining the first post-wash concentrate from step (G) with the bulk solution from step (D), thereby forming a concentrated IgG composition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **Figure 1** is a graphic illustration of the new ultrafiltration/diafiltration system.

DEFINITIONS

[0016] An "**antibody**" refers to a polypeptide substantially encoded by an immunoglobulin gene or immunoglobulin genes, or fragments thereof, which specifically bind and recognize