formulations are unstable in the absence of the disaccharide, as evidenced by the high level of aggregate formation upon reconstitution when formulated with histidine alone.

[0008] U.S. Patent Application Publication No. 2010/0015157 describes the formulation of monoclonal antibodies with low concentrations of histidine acetate buffer (*i.e.*, 10-20 mM) at pH 5.5 to 6.5 with non-ionic surfactants and/or disaccharides (*i.e.*, sucrose or trehalose). However, the monoclonal antibody formulations are unstable in the absence of a non-ionic surfactants and/or disaccharides, as evidenced by the high turbidity and level of antibody aggregation seen in compositions formulated with histidine alone.

[0009] As such, there is a need in the art for formulations and methods of formulation that stabilize these labile therapeutic proteins in aqueous compositions at mildly acidic to neutral pH. The present invention satisfies these and other needs by, among other aspects, providing immunoglobulin compositions formulated with histidine at mild acidic to neutral pH that stabilize labile therapeutic proteins.

BRIEF SUMMARY ~~OF INVENTION~~

[0010] ~~[0008]~~ The present disclosure~~invention~~ is based in part by the surprising finding that the inclusion of histidine in an immunoglobulin composition formulated at mildly acidic to neutral pH significantly stabilizes the formulation.

[0011] Advantageously, the storage-stable aqueous immunoglobulin compositions provided herein remain stable for long periods at temperatures (*e.g.*, for a year or longer) without the inclusion of additional excipients such as non-ionic surfactants and saccharides.

[0012] In contrast to previously described monoclonal antibody compositions, that are formulated using low concentrations of histidine (*i.e.*, from 5 mM to 20 mM) at mildly acidic to neutral pH, the aqueous immunoglobulin compositions provided herein, which are formulated with moderate to high concentrations of histidine (*i.e.*, from 50 mM to 500 mM), are stable at mildly acidic to neutral pH in the absence of surfactants (*e.g.*, non-ionic surfactants such as polysorbate 80) and saccharides (*e.g.*, disaccharides such as sucrose and trehalose). The use of fewer components for the formulation of immunoglobulins may be beneficial, as acute renal failure or insufficiency has been linked to the use of IVIG formulated with sucrose, maltose, and

glucose (MMWR Morb Mortal Wkly Rep. 1999 Jun 25;48(24):518-21; Kwan *et al.* Hong Kong Med J. 2005 Feb;11(1):45-9). Similarly, sever hypersensitivity reactions may occur in patients administered IVIG formulated with polysorbate 80. In fact, Hizentra® (Immune Globulin Subcutaneous (Human), 20% Liquid; CSL Behring AG, Bern, Switzerland) is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of Hizentra, such as polysorbate 80 (Hizentra Prescribing Information). Furthermore, the ability to stably formulate immunoglobulins at mildly acidic to neutral pH allows for the manufacture of pharmaceutical compositions that may be administered subcutaneously (SQ) or intramuscularly (IM) without the pain and potential for tissue damage that is associated with the SQ and IM administration of compositions formulated at acidic pH.

[0013] In one embodimentaspect, the present disclosureinvention provides a storage stable, aqueous immunoglobulin composition comprising: (a) an immunoglobulin; (b) from 50 mM to 500 mM histidine; (c) from 0 mM to 10 mM of an alkali metal cation; and (d) a pH from 5.5 to 7.0.

[0014] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 150 mM to 350 mM histidine.

[0015] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 225 mM to 275 mM histidine. Hence, in an aspect, there is provided a storage stable, aqueous immunoglobulin composition comprising: (a) an immunoglobulin (b) from 225 mM to 275 mM histidine; (c) from 0 mM to 10 mM of an alkali metal cation; and (d) a pH from 5.5 to 7.0, wherein the composition is stable for at least 6 months when stored at from 28°C to 32°C, and wherein the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state remains below 2%, and wherein the composition does not contain a surfactant or sugar.

[0016] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 0 mM to 1 mM of an alkali metal cation.

[0017] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 10 mM to 400 mM chloride ions.

[0018] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 100 mM to 200 mM chloride ions.

[0019] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the pH of the composition is from 5.5 to 6.5.

[0044] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 6 months when stored at from 38°C to 42°C.

[0045] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 6 months when stored at from 28°C to 32°C.

[0046] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 1 year when stored at from 28°C to 32°C.

[0047] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 2 years when stored at from 28°C to 32°C.

[0048] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state remains below 2%.

[0049] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state is from 0% to 2% and the percentage of immunoglobulin in the monomeric state is from 85% to 100%.

[0050] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, a composition having the same components, but formulated at pH 4.8, is stable for less than 1 month when stored at from 38°C to 42°C.

[0051] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, a composition having the same components, but formulated at pH 4.8, is stable for less than 6 months when stored at from 28°C to 32°C.

[0052] In one embodiment~~aspect~~, the present disclosure~~invention~~ provides a method for stabilizing an immunoglobulin composition, the method comprising formulating the composition at a pH between 5.5 and 7.0, wherein the formulated composition comprises: (a) an immunoglobulin; (b) from 50 mM to 500 mM histidine; and (c) from 0 mM to 10 mM of an alkali metal cation.