degradation over time can adversely impact the protective effect that polysorbates exhibit in protein-containing formulations.

Proteins undergo varying degrees of degradation during purification and storage, wherein oxidation (including, light-induced oxidation) is one of the major degradation pathways that has a destructive effect on protein stability and potency. Oxidative reactions cause destruction of amino acid residues, peptide bond hydrolysis, and hence protein instability due to alteration of the protein's tertiary structure and protein aggregation (Davies, J. Biol. Chem. 262: 9895-901 (1987)). Oxidation of protein pharmaceuticals have been reviewed by Nguyen (Chapter 4 in Formulation and Delivery of Protein and Peptides (1994)), Hovorka, (J. Pharm Sci. 90:25369 (2001)) and Li (Biotech Bioengineering 48:490-500 (1995)).

Given the above, it is evident that there is a need for the identification of compositions useful for enhancing the stability and preventing the aggregation and/or oxidation of proteins in protein-containing formulations.

SUMMARY ~~OF THE INVENTION~~

The present disclosure~~invention~~ is based upon the novel finding that certain alkylglycoside compositions are useful for stabilizing and/or reducing aggregation or immunogenicity of antibodies or other proteins in therapeutically useful formulations. Moreover, the present disclosure~~invention~~ is further based upon the novel finding that certain alkylglycoside compositions are useful for preventing the oxidation of amino acid residues, particularly tryptophan residues, on antibodies or other proteins in therapeutically useful formulations. More specifically, one embodiment~~aspect~~ of the present disclosure~~invention~~ is directed to methods of using alkylglycosides having a critical micelle concentration (CMC) value of at least 1.0 mM as protein stabilizing, or aggregation-reducing, agents. In certain embodiments of the present invention, the alkylglycoside composition is used in the antibody- or other protein-containing formulation at a concentration that is below its respective CMC value.

In one aspect, there is provided an aqueous composition of matter comprising an antibody and an alkylglycoside having a CMC value of about 1.0 mM or greater in water at 25°C, wherein the alkylglycoside is present at a concentration that is lower than the CMC value of the alkylglycoside in water at 25°C.

Accordingly, in one embodimentaspect, the present disclosureinvention relates to a composition of matter comprising a protein and an alkylglycoside having a CMC value of about 1.0 mM or greater in water at 25°C. In certain embodiments, the protein present in the composition of matter is an antibody, which may optionally be a monoclonal antibody. In yet other embodiments, the alkylglycoside is selected from the group consisting of n-hexyl-β-D-glucopyranoside, n-heptyl-β-D-glucopyranoside, n-octyl-β-D-glucopyranoside, n-nonyl-β-D-glucopyranoside, n-decyl-β-D-glucopyranoside, 3-

cyclohexyl-1-propyl-β-D-glucoside, 3-cyclohexyl-1-butyl-β-D-glucoside, n-hexyl-β-D-maltopyranoside, n-octyl-β-D-maltopyranoside, n-nonyl-β-D-maltopyranoside, n-decyl-β-D-maltopyranoside, cyclohexyl-methyl-β-D-maltoside, 2-cyclohexyl-ethyl-β-D-maltoside, 3-cyclohexyl-propyl-β-D-maltoside, 4-cyclohexyl-butyl-β-D-maltoside, and 5-cyclohexyl-pentyl-β-D-maltoside. In yet other embodiments, the composition of matter comprises an agitation-induced aggregation inhibiting amount or an oxidation preventing amount of the alkylglycoside. In yet another embodiment, the alkylglycoside is present in the composition of matter at a concentration that is lower than the CMC value of the alkylglycoside in water at 25°C. the composition of matter may be aqueous, may be stable at a temperature of about 2-8°C for at least one year, and/or may be stable at a temperature of about 30°C for at least one month. Optionally, the composition of matter is not lyophilized and is not subjected to prior lyophilization or may be a reconstituted lyophilized formulation.

In another embodiment~~aspect~~, the present disclosure~~invention~~ is directed to an article of manufacture comprising a container holding the above described composition of matter.

Yet another embodiment~~aspect~~ of the present disclosure~~invention~~ is directed to a making a pharmaceutical formulation comprising preparing the above described composition of matter and evaluating the physical stability, chemical stability, or biological activity of the protein in the composition of matter.

In one aspect, there is provided a method of inhibiting agitation-induced aggregation of an antibody present in an first aqueous solution, said method comprising the step of adding to said first aqueous solution an agitation-induced aggregation inhibiting amount of an alkylglycoside having a CMC value of about 1.0 mM or greater in water at 25°C, wherein the alkylglycoside is added to a final concentration that is lower than the CMC value of the alkylglycoside in water at 25°C, thereby providing a second aqueous solution.

Yet another embodiment~~aspect~~ of the present disclosure~~invention~~ is directed to a method of inhibiting agitation-induced aggregation of a protein present in an first aqueous solution, wherein the method comprises the step of adding to the first aqueous solution an agitation-induced aggregation inhibiting amount of an alkylglycoside having a CMC value of about 1.0 mM or greater in water at 25°C, thereby providing a second aqueous solution.

In one aspect, there is provided a method of preventing oxidation of an antibody present in an first aqueous solution, said method comprising the step of adding to said first aqueous solution an oxidation preventing amount of an alkylglycoside having a CMC value of about 1.0 mM or greater in water at 25°C, wherein the alkylglycoside is added to a final concentration that is lower than the CMC value of the alkylglycoside in water at 25°C, thereby providing a second aqueous solution.

Yet another embodiment~~aspect~~ of the present disclosure~~invention~~ is directed to a method of preventing the oxidation of a protein present in an first aqueous solution, wherein the method comprises the step of adding to the first aqueous solution an oxidation inhibiting amount of an alkylglycoside having a CMC value of about 1.0 mM or greater in water at 25°C, thereby providing a second aqueous solution.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effect of certain surfactants on aggitation-induced aggregation of an anti-MUC16 monoclonal antibody in aqueous solution.