[0025] **Figure 9** shows that the effect of $CaCl_2$ is similar at pH 7.3 and pH 6.5.

DETAILED DESCRIPTION OF THE INVENTION

Definition of terms

[0026] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton, et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY (2d ed. 1994); THE CAMBRIDGE DICTIONARY OF SCIENCE AND TECHNOLOGY (Walker ed., 1988); THE GLOSSARY OF GENETICS, 5TH ED., R. Rieger, et al. (eds.), Springer Verlag (1991); and Hale and Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY (1991).

[0027] Each publication, patent application, patent, and other reference cited herein is incorporated by reference in its entirety to the extent that it is not inconsistent with the present disclosure.

~~[0028] It is noted here that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.~~

[0029] As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0030] The term "comprising," with respect to a peptide compound, means that a compound may include additional amino acids at either or both amino and carboxy termini of the given sequence. Of course, these additional amino acids should not significantly interfere with the activity of the compound. With respect to a composition of the instant invention, the term "comprising" means that a composition may include additional components. These additional components should not significantly interfere with the activity of the composition.

[0031] The term "pharmacologically active" means that a substance so described is determined to have activity that affects a medical parameter (e.g., but not limited to blood pressure, blood cell count, cholesterol level) or disease state (e.g., but not limited to cancer, autoimmune disorders).

[0032] As used herein the terms "express," "expressing" and "expression" mean allowing or causing the information in a gene or DNA sequence to become manifest, for example, producing a

CLAIMS

1. A stable liquid pharmaceutical formulation of a recombinant von Willebrand Factor (rVWF) comprising: (a) a rVWF; (b) a buffering agent; (c) one or more salts;

wherein said rVWF in the pharmaceutical formulation causes agglutination of stabilized platelets in the presence of ristocetin, is stable for at least 26 weeks at 4°C and comprises a polypeptide that has a molecular weight of 250 kDa selected from the group consisting of:

a) the amino acid sequence set out in SEQ ID NO: 3;

b) a biologically active analog or variant of a);

c) a polypeptide encoded by the polynucleotide set out in SEQ ID NO: 1;

d) a biologically active analog or variant of c); and

e) a polypeptide encoded by a polynucleotide that hybridizes to the polynucleotide set out in SEQ ID NO: 1 under moderately stringent hybridization conditions;

wherein said buffering agent is citrate at a concentration of 0.1 mM to 500 mM,

wherein the pH is in a range of 3.0 to 9.0; and wherein said salt is at a concentration of 0.5 mM to 500 mM.

2. The formulation of claim 1, wherein the rVWF retains at least 50% agglutination ability of stabilized platelets in the presence of ristocetin at 26 weeks compared to the same material measured at the commencement of storage.

3. The formulation of claim 1, wherein the formulation does not include glutathione.

4. The formulation of any one of claims 1 to 3, wherein the rVWF comprises the amino acid sequence set out in SEQ ID NO: 3.

5. The formulation of any one of claims 1 to 4, wherein the buffering agent is at a concentration range of 0.5 mM to 100 mM.

6. The formulation of any one of claims 1 to 5, wherein the buffering agent is at a concentration range of 1 mM to 50 mM.

~~7. The formulation of any one of claims 1 to 6, wherein the buffering agent is at a concentration range of 5 mM to 30 mM~~

~~8. The formulation of any one of claims 1 to 7, wherein the buffering agent is at a concentration of 15 mM.~~

~~9. The formulation of any one of claims 1 to 3, wherein a first buffering agent and a second buffering agent are each at a concentration of 3.3 mM.~~

~~10. The formulation of any one of claims 1 to 9, wherein the salt is at a concentration range of 0.5 to 300 mM.~~

~~11. The formulation of any one of claims 1 to 10, wherein the salt is at a concentration range of 1 mM to 100 mM.~~

~~12. The formulation of any one of claims 1 to 11, wherein the salt is at a concentration range of 10 mM to 50 mM.~~

~~13. The formulation of any one of claims 1 to 12, wherein the salt is at a concentration of 10 mM.~~

~~14. The formulation of any one of claims 1 to 13, wherein a first salt is at a concentration of 10 mM and a second salt is at a concentration of 100 mM.~~

CLAIMS

~~15.~~ 1. A stable liquid pharmaceutical formulation of a recombinant von Willebrand Factor (rVWF) comprising: (a) a rVWF; (b) a buffering agent; and (c) one or more salts,

wherein said rVWF in the pharmaceutical formulation causes agglutination of stabilized platelets in the presence of ristocetin, is stable for at least 26 weeks at 4°C and comprises a polypeptide that has a molecular weight of approximately 250 kDa selected from the group consisting of:

a) the amino acid sequence set out in SEQ ID NO: 3;

b) a biologically active analog or variant of a);

c) a polypeptide encoded by the polynucleotide set out in SEQ ID NO: 1;

d) a biologically active analog or variant of c); and

e) a polypeptide encoded by a polynucleotide that hybridizes to the polynucleotide set out in SEQ ID NO: 1 under moderately stringent hybridization conditions;

wherein the buffering agent is citrate at a concentration of 15 mM, wherein the pH is in a range of 3.0 to 9.0; and wherein a first salt is sodium chloride at a concentration of 100 mM and a second salt is calcium chloride at a concentration of 10 mM.

~~16. The formulation of any one of the preceding claims, wherein the buffering agent is sodium citrate.~~

~~17. The formulation of any one of the preceding claims, wherein the pH is in the range of 5.5 to 8.5.~~

~~18. The formulation of any one of the preceding claims, wherein the pH is in the range of 6.0 to 8.0.~~

~~19. The formulation of any one of the preceding claims, wherein the pH is in the range of 6.5 to 7.5.~~

~~20. The formulation of any one of the preceding claims, wherein the pH is 7.0.~~

~~21. The formulation of claim 19, wherein a first salt is at a concentration of 30 mM and a second salt is at a concentration of 0.56 mM.~~

RECOMBINANT VWF FORMULATIONS

Abstract

The present invention provides long-term stable pharmaceutical formulations of recombinant von-Willebrand Factor (rVWF) and methods for making and administering said formulations.

(No suitable figure)