also exhibit and promote the long-term stability of the AAV, minimizing loss of AAV potency during the manufacture, packaging, and storage processes. The formulations should furthermore prevent adsorption to the surfaces of the containers in which the AAV are packaged and stored and of the machinery used during manufacture. Though the efforts to design such AAV formulations have been great, there still remains a need for improved AAV formulations.

SUMMARY

[0005] The present disclosure provides formulations compatible for human administration which address the unmet needs described above. Advantageously, in some examples, the formulations are suitable for long-term storage of AAV, minimizing loss of AAV potency, and advantageously prevent visible particle formation and prevent adsorption to the surfaces of the containers in which the AAV are packaged and stored and of the machinery used during manufacture. In one aspect, the present disclosure refers to A storage stable pharmaceutical composition comprising adeno-associated virus (AAV) and a buffering composition consisting of: (i) about 5 mM to about 25 mM of a buffering agent is selected from the group consisting of histidine, arginine, lysine and a combination thereof; (ii) about 50 mM to about 150 mM of a pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, ammonium salt, potassium salt, and a combination thereof; (iii) about 0.001% (w/v) to about 0.01% (w/v) of a non-ionic surfactant; and (iv) about 1% to about 10% (w/v) of is one or more ingredient selected from the group consisting of a sugar, a sugar alcohol, and a combination thereof, wherein the buffering composition has a pH of about 6.9 to about 7.7. In another aspect, the present disclosure refers to the use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a bleeding disorder in a subject. In other examples, the pharmaceutical composition of the present disclosure comprises: adeno-associated virus (AAV) and about 5 mM to about 25 mM of a buffering agent, about 0 mM to about 150 mM of a pharmaceutically acceptable salt, about 0.001% (w/v) to about 0.01% (w/v) of a non-ionic surfactant, and about 1% (w/v) to about 10% (w/v) of a sugar or sugar alcohol. In certain examples, the formulation comprises about 50 mM to

about 150 mM of a pharmaceutically acceptable salt. In certain examples, the formulation comprises about 0 mM to less than about 100 mM of a pharmaceutically acceptable salt. In certain examples, the formulation comprises about 30 mM to less than about 100 mM of a pharmaceutically acceptable salt. In certain examples, the formulation comprises about 20 mM to about 40 mM of a pharmaceutically acceptable salt.

[0006] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV (e.g., AAV8), about 5 mM to about 25 mM L-histidine, about 0 mM to about 150 mM sodium chloride, about 0.001% (w/v) to about 0.01% (w/v) polysorbate 80 (PS80), and about 1% to about 10% (w/v) sucrose, trehalose, mannitol, or a combination thereof. In certain examples, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain examples, the formulation

about 150 mM of a pharmaceutically acceptable salt. In certain examples, the formulation comprises about 0 mM to less than about 100 mM of a pharmaceutically acceptable salt. In certain examples, the formulation comprises about 30 mM to less than about 100 mM of a pharmaceutically acceptable salt. In certain examples, the formulation comprises about 20 mM to about 40 mM of a pharmaceutically acceptable salt.

[0006] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV (e.g., AAV8), about 5 mM to about 25 mM L-histidine, about 0 mM to about 150 mM sodium chloride, about 0.001% (w/v) to about 0.01% (w/v) polysorbate 80 (PS80), and about 1% to about 10% (w/v) sucrose, trehalose, mannitol, or a combination thereof. In certain examples, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain examples, the formulation

comprises about 0 mM to less than about 100 mM sodium chloride. In certain examples, the formulation comprises about 30 mM to less than about 100 mM sodium chloride. In certain examples, the formulation comprises about 20 mM to about 40 mM sodium chloride.

[0007] In some examples, the disclosure describes a liquid formulation. In certain embodiments, the formulation is lyophilized from a liquid formulation.

[0008] In certain examples, the lyophilized pharmaceutical composition of the present disclosure is lyophilized from a liquid formulation comprising: AAV (e.g., AAV8), about 5 mM to about 25 mM L-histidine, about 0 mM to about 150 mM sodium chloride, about 0.001% (w/v) to about 0.01% (w/v) polysorbate 80 (PS80), about 30 mM to about 70 mM glycine, and about 1% to about 10% (w/v) sucrose, trehalose, mannitol, or a combination thereof. In certain examples, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain examples, the formulation comprises about 0 mM to less than about 100 mM sodium chloride. In certain examples, the formulation comprises about 30 mM to less than about 100 mM sodium chloride. In certain examples, the formulation comprises about 20 mM to about 40 mM sodium chloride.

[0009] Methods of preparing a pharmaceutical composition comprising AAV are further provided herein. In exemplary aspects, the method comprises combining about 5 mM to about 25 mM L-histidine, about 0 mM to about 150 mM sodium chloride, about 0.001% (w/v) to about 0.01% (w/v) polysorbate 80 (PS80), about 1% (w/v) to about 10% (w/v) sucrose, trehalose, mannitol, or a combination thereof and AAV, thereby obtaining a pharmaceutical composition comprising AAV. In certain examples, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain embodiments, the formulation comprises about 0 mM to less than about 100 mM sodium chloride. In certain examples, the formulation comprises about 30 mM to less than about 100 mM sodium chloride. In certain examples, the formulation comprises about 20 mM to about 40 mM sodium chloride.

[0010] Methods of treating a subject for a disorder treatable by gene therapy are provided by the present disclosure. In certain examples, the method comprises

administering to the subject a pharmaceutical composition as described herein in an amount effective to treat the disorder.

[0011] Methods of storing a composition comprising AAV are moreover provided herein. In certain examples, the method comprises combining about 5 mM to about 25 mM L-histidine, about 0 mM to about 150 mM sodium chloride, about 0.001% (w/v) to about 0.01% (w/v) polysorbate 80 (PS80), about 1% (w/v) to about 10% (w/v) sucrose, trehalose, mannitol, or a combination thereof and AAV. In certain examples, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain examples, the formulation comprises about 0 mM to less than about 100 mM sodium chloride. In certain examples, the formulation comprises about 30 mM to less than about 100 mM sodium chloride. In certain examples, the formulation comprises about 20 mM to about 40 mM sodium chloride.

[0012] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 20 mM L-histidine, about 70 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), and about 5% (w/v) sucrose. In some examples, the invention provides a liquid formulation. In certain embodiments, the formulation is lyophilized from a liquid formulation.

[0013] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 20 mM L-histidine, about 60 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 35 mM trehalose, and about 110 mM mannitol. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0014] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 100 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0015] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 80 mM sodium chloride,

about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0016] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 70 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0017] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 60 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0018] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 50 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0019] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 40 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0020] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 30 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0021] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 20 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0022] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 10 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0023] In certain examples, the pharmaceutical composition of the present disclosure comprises: AAV and about 10 mM L-histidine, about 0 mM sodium chloride, about 0.005% (w/v) polysorbate 80 (PS80), about 5% (w/v) trehalose, and about 50 mM glycine. In some examples, the invention provides a liquid formulation. In certain examples, the formulation is lyophilized from a liquid formulation.

[0024] Generally, the AAV formulations provided herein are suitable for pharmaceutical administration. In certain examples, the AAV is AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, or AAV10. In certain examples, the AAV is AAV 2, AAV 5, AAV 8, or AAV 9. In certain examples, the AAV is AAV8.

DETAILED DESCRIPTION

[0025] The present disclosure provides formulations, e.g., pharmaceutical compositions, compatible for human or veterinarian administration which also are suitable for long-term storage of AAV and minimizing loss of AAV potency. The formulations provided herein are advantageous, because the formulations prevent visible particle formation and also prevent adsorption to the surfaces of the containers in which the AAV are packaged and stored, and prevent adsorption to the machinery used during manufacture. In certain embodiments, the pharmaceutical compositions provided herein retain significant AAV activity when stored for extended periods of time. In certain embodiments, the pharmaceutical compositions provided herein reduce or retard degradation and/or aggregation.

WHAT IS CLAIMED:

1. A storage stable pharmaceutical composition comprising adeno-associated virus (AAV) and a buffering composition consisting of:

(i) about 5 mM to about 25 mM of a buffering agent is selected from the group consisting of histidine, arginine, lysine and a combination thereof;

(ii) about 50 mM to about 150 mM of a pharmaceutically acceptable salt is selected from the group consisting of a sodium salt, ammonium salt, potassium salt, and a combination thereof;

(iii) about 0.001% (w/v) to about 0.01% (w/v) of a non-ionic surfactant; and

(iv) about 1% to about 10% (w/v) of is one or more ingredient selected from the group consisting of a sugar, a sugar alcohol, and a combination thereof,

wherein the buffering composition has a pH of about 6.9 to about 7.7.

2. The pharmaceutical composition of claim 1, wherein the buffering composition has a pH of about 7.0 or about 7.5.

3. The pharmaceutical composition of claim 1, wherein the buffering agent is L-histidine.

4. The pharmaceutical composition of claim 3, wherein the buffering agent is L-histidine in an amount from about 10 mM to about 20 mM.

5. The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable salt is sodium chloride.

6. The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable salt is sodium chloride in an amount from about 50 mM to about 120 mM sodium chloride.

7. The pharmaceutical composition of claim 1, wherein the non-ionic surfactant is polysorbate 80 (PS80).

8. The pharmaceutical composition of claim 7, wherein the non-ionic surfactant is PS80 in an amount from about 0.0025% to about 0.0075% (w/v).

9. The pharmaceutical composition of claim 1, wherein the sugar is sucrose, trehalose, or a combination thereof.

10. The pharmaceutical composition of claim 9, wherein the sugar is about 1% (w/v) to about 5% (w/v) sucrose, trehalose, or a combination thereof.

11. The pharmaceutical composition of claim 1, further comprising one or more ingredient(s) selected from the group consisting of glycine, mannitol, or both glycine and mannitol.

12. The pharmaceutical composition of claim 11, wherein the ingredient is glycine in an amount of about 35 mM to about 65 mM.

13. The pharmaceutical composition of claim 11, wherein the ingredient is mannitol in an amount from about 80 mM to about 120 mM.

14. The pharmaceutical composition of claim 1, wherein the buffering composition does not comprise dextran.

15. The pharmaceutical composition of claim 1, wherein the buffering composition is:

(i) about 20 mM L-histidine,

(ii) about 70 mM sodium chloride,

(iii) about 0.005% (w/v) polysorbate 80 (PS80), and

(iv) about 5% (w/v) sucrose.

16. The pharmaceutical composition of claim 1, wherein the buffering composition is:

(i) about 10 mM L-histidine,

(ii) about 100 mM sodium chloride,

(iii) about 0.005% (w/v) polysorbate 80 (PS80),

(iv) about 5% (w/v) trehalose, and

(v) about 50 mM glycine.

17. The pharmaceutical composition of claim 1, wherein the pharmaceutical acceptable salt is sodium chloride in an amount selected from about 80 mM, about 70 mM, about 60 mM, or about 50 mM.

18. The pharmaceutical composition of claim 1, wherein the buffering composition is

(i) about 20 mM L-histidine,

(ii) about 60 mM sodium chloride,

(iii) about 0.005% (w/v) polysorbate 80 (PS80),

(iv) about 35 mM trehalose, and

(v) about 110 mM mannitol.

19. The pharmaceutical composition of claim 1, wherein the AAV is at least one of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, or AAV10

20. The pharmaceutical composition of claim 1, wherein the composition is liquid.

21. The pharmaceutical composition of claim 1, wherein the composition is lyophilized.

22. Use of the pharmaceutical composition of any one of claims 1 to 21 in the manufacture of a medicament for treating a bleeding disorder in a subject.

23. The pharmaceutical composition of claim 8, wherein the pharmaceutically acceptable salt is sodium chloride in an amount from about 60 mM to about 100 mM.

24. The pharmaceutical composition of claim 23, wherein the pharmaceutically acceptable salt is sodium chloride in an amount from about 60 mM to about 80 mM.