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 ~~embodiments~~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 ~~exemplary aspects~~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~~embodiments~~, the formulation comprises about 50 mM to

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

[0006] In exemplary aspectscertain 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 examplesembodiments, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain examplesembodiments, the formulation

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

[0006] In ~~exemplary aspects~~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~~embodiments~~, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain examples~~embodiments~~, the formulation

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

[0007] In some examplesembodiments, the invention providesdisclosure describes a liquid formulation. In certain embodiments, the formulation is lyophilized from a liquid formulation.

[0008] In certain examplesaspects, 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 examplesembodiments, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain examplesembodiments, the formulation comprises about 0 mM to less than about 100 mM sodium chloride. In certain examplesembodiments, the formulation comprises about 30 mM to less than about 100 mM sodium chloride. In certain examplesembodiments, 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 examplesembodiments, 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 examplesembodiments, the formulation comprises about 30 mM to less than about 100 mM sodium chloride. In certain examplesembodiments, 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 exemplary aspectscertain 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 ~~exemplary aspects~~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~~embodiments~~, the formulation comprises about 50 mM to about 150 mM sodium chloride. In certain examples~~embodiments~~, the formulation comprises about 0 mM to less than about 100 mM sodium chloride. In certain examples~~embodiments~~, the formulation comprises about 30 mM to less than about 100 mM sodium chloride. In certain examples~~embodiments~~, the formulation comprises about 20 mM to about 40 mM sodium chloride.

[0012] In certain examples~~embodiments~~, 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~~embodiments~~, the invention provides a liquid formulation. In certain embodiments, the formulation is lyophilized from a liquid formulation.

[0013] In certain examples~~embodiments~~, 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~~embodiments~~, the invention provides a liquid formulation. In certain examples~~embodiments~~, the formulation is lyophilized from a liquid formulation.

[0014] In certain examples~~embodiments~~, 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~~embodiments~~, the invention provides a liquid formulation. In certain examples~~embodiments~~, the formulation is lyophilized from a liquid formulation.

[0015] In certain examples~~embodiments~~, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

[0016] In certain examplesembodiments, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

[0017] In certain examplesembodiments, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

[0018] In certain examplesembodiments, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

[0019] In certain examplesembodiments, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

[0020] In certain examplesembodiments, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

[0021] In certain examplesembodiments, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

[0022] In certain examplesembodiments, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

[0023] In certain examplesembodiments, 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 examplesembodiments, the invention provides a liquid formulation. In certain examplesembodiments, the formulation is lyophilized from a liquid formulation.

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

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

~~2. A pharmaceutical composition comprising adeno-associated virus (AAV) and:~~

~~(i) about 5 mM to about 25 mM buffering agent;~~

~~(ii) less than about 100 mM pharmaceutically acceptable salt;~~

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

~~(iv) about 1% to about 10% (w/v) sugar, sugar alcohol, or combination thereof.~~

~~3.~~2. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, wherein the ~~pharmaceutical~~ buffering composition has a pH of ~~about 6.9 to about 7.7, optionally,~~ about 7.0 or about 7.5.

~~4.~~3. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, wherein the buffering agent is L-histidine.

~~5.~~4. The pharmaceutical composition of claim ~~4~~3, wherein the buffering agent is L-histidine in an amount from~~comprising about 5 mM to about 25 mM or~~ about 10 mM to about 20 mM ~~L-histidine~~.

~~6.~~5. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, wherein the pharmaceutically acceptable salt is ~~a~~ sodium ~~salt~~chloride~~, ammonium salt or potassium salt~~.

~~7. The pharmaceutical composition of claim 6, comprising about 50 mM to about 120 mM sodium chloride.~~

~~8.~~6. The pharmaceutical composition of claim ~~1~~6 ~~or claim 7~~, wherein the pharmaceutically acceptable salt is sodium chloride in an amount from about 50mM to about 120 mM ~~comprising about 0 mM to about 100 mM, about 0 mM to about 60 mM, 30 mM to about 100 mM, 30 mM to about 80 mM, or 30 mM to about 60 mM sodium chloride~~.

~~9. The pharmaceutical composition or any one of claims 6-8, comprising about 60 mM to about 100 mM or about 60 mM to about 80 mM sodium chloride.~~

~~10.~~7. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, wherein the non-ionic surfactant is polysorbate 80 (PS80).

~~11.~~8. The pharmaceutical composition of claim ~~10~~7, ~~comprising~~ wherein the non-ionic surfactant is PS80 in an amount from about 0.0025% to about 0.0075% (w/v) ~~PS80~~.

~~12.~~9. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, wherein the sugar is sucrose, trehalose, or a combination thereof.

~~13.~~10. The pharmaceutical composition of claim ~~12~~9, wherein the sugar is ~~comprising~~ about 1% (w/v) to about 5% (w/v) sucrose, trehalose, or a combination thereof.

~~14. The pharmaceutical composition of claim 12 or claim 13, wherein the trehalose is trehalose dihydrate.~~

~~15.~~11. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, further comprising one or more ingredient(s) selected from the group consisting of glycine, mannitol, or both glycine and mannitol.

~~16.~~12. The pharmaceutical composition of claim ~~15~~11, wherein the ingredient is glycine in an amount of ~~comprising~~ about 35 mM to about 65 mM ~~glycine~~.

~~17. The pharmaceutical composition as in any of the preceding claims, further comprising mannitol.~~

~~18.~~13. The pharmaceutical composition of claim ~~17~~11, ~~comprising~~ wherein the ingredient is mannitol in an amount from about 80 mM to about 120 mM ~~mannitol~~.

~~19.~~14. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, ~~which~~ wherein the buffering composition does not comprise dextran.

~~20. The pharmaceutical composition as in any of the preceding claims, comprising glycine or mannitol.~~

~~21. The pharmaceutical composition as in any of claims 10-20, wherein the PS80 is Super Refined™ PS80.~~

~~22.~~15. ~~A~~ The pharmaceutical composition ~~comprising adeno-associated virus (AAV) and~~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.

~~23.~~16. ~~A~~ The pharmaceutical composition ~~comprising adeno-associated virus (AAV) and~~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.

~~24. A pharmaceutical composition comprising adeno-associated virus (AAV) and~~

~~(i) about 10 mM L-histidine,~~

~~(ii) less than 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.~~

~~25.~~17. The pharmaceutical composition of ~~any one of claims 1-21 or 24~~claim 1, wherein the pharmaceutical acceptable salt is sodium chloride in an amount selected from ~~comprising~~ about 80 mM, about 70 mM, about 60 mM, or about 50 mM ~~sodium chloride~~.

~~26. The pharmaceutical composition of any one of claims 1-21 or 24, comprising about 70 mM sodium chloride.~~

~~27. The pharmaceutical composition of any one of claims 1-21 or 24, comprising about 60 mM sodium chloride.~~

~~28. The pharmaceutical composition of any one of claims 1-21 or 24, comprising about 50 mM sodium chloride.~~

~~29. The pharmaceutical composition of any one of claims 1-21 or 24, comprising about 40 mM sodium chloride.~~

~~30. The pharmaceutical composition of any one of claims 1-21 or 24, comprising about 30 mM sodium chloride.~~

~~31. The pharmaceutical composition of any one of claims 2-21 or 24, comprising about 0 mM sodium chloride.~~

~~32.~~18. ~~A~~ The pharmaceutical composition of claim 1, wherein the buffering composition is~~comprising adeno-associated virus (AAV) and~~

(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.

~~33. The pharmaceutical composition as in any of the preceding claims, comprising AAV.~~

~~34.~~19. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, ~~comprising~~ wherein the AAV is at least one of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, or AAV10

~~35. The pharmaceutical composition as in any of the preceding claims, comprising AAV8.~~

~~36.~~20. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, wherein the composition is liquid.

~~37.~~21. The pharmaceutical composition ~~as in any of the preceding claims~~of claim 1, wherein the composition is lyophilized.

~~38. The pharmaceutical composition as in any of the preceding claims, wherein the composition is present in a unit dosage container.~~

~~39. The pharmaceutical composition of claim 38, wherein the unit dosage container is a vial.~~

~~40. The pharmaceutical composition of claim 39, wherein the vial is a sealed glass vial.~~

~~41. A method of preparing a pharmaceutical composition comprising adeno-associated virus (AAV), comprising combining the buffering agent, the pharmaceutically acceptable salt, the non-ionic surfactant, and the sugar, sugar alcohol, or combinations thereof of the pharmaceutical composition of claims 1-40, thereby obtaining a pharmaceutical composition comprising AAV.~~

~~42. A method of preparing a pharmaceutical composition comprising adeno-associated virus (AAV), comprising 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, or a combination thereof and AAV, thereby obtaining a pharmaceutical composition comprising AAV.~~

~~43.~~22. Use of the pharmaceutical composition of any one of claims 1 to 21 in the manufacture of a medicament for~~A method of~~ treating a bleeding disorder in a subject~~, comprising administering to the subject a pharmaceutical composition of any one of claims 1-40 in an amount effective to treat a disorder or disease~~.

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.

~~44. The method of claim 43, wherein the disorder or disease is a bleeding disorder.~~

~~45. A method of storing a composition comprising AAV, comprising combining the buffering agent, the pharmaceutically acceptable salt, the non-ionic surfactant, and the sugar, sugar alcohol, or combinations thereof of the pharmaceutical composition of claims 1-40.~~

~~46. A method of storing a composition comprising AAV, comprising 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% to about 10% (w/v) sucrose, trehalose, or combination thereof and AAV.~~

~~47. The method of claim 42 or claim 46, comprising about 50 mM to about 150 mM sodium chloride.~~

~~48. The method of claim 42 or claim 46, comprising about 30 mM to less than about 100 mM sodium chloride.~~

~~49. The method of any one of claim 42 or 46-48, comprising about 0 mM to less than about 100 mM sodium chloride.~~

~~50. The method of any one of claim 42 or 46-49, comprising about 30 mM sodium chloride.~~

~~51. The method of any one of claim 42 or 46-49, comprising about 60 mM sodium chloride.~~

~~52. The method of any one of claim 42 or 46-49, comprising about 0 mM sodium chloride.~~