

[0035] Surprisingly it has been found that a chloride salt of TAT-NR2B9c confers significantly greater stability in the lyophilized form than an acetate salt of TAT-NR2B9c in the same formulation, or an acetate salt of TAT-NR2B9c lyophilized from saline. The chloride salt can remain sufficiently stable for clinical use even with storage at summer time ambient temperatures reaching or even exceeding 37°C for several years. The greater stability of the chloride salt over acetate more than compensates for any greater effort or reduced yield required in replacing trifluoroacetate as a salt. The present invention provides lyophilized formulations of active agents, particularly of TAT-NR2B9c as a chloride salt. Such formulations are stable at ambient temperature (e.g., at least 20°C) thus facilitating maintenance of supplies of such a formulation in ambulances or the like or with emergency personnel for administration at the scene of illness or accident or between such scene and a medical facility.

[0036] Lyophilized formulations are prepared from a prelyophilized formulation comprising an active agent, a buffer, a bulking agent and water. Other components, such as cryo or lyopreservatives, a tonicity agent pharmaceutically acceptable carriers and the like may or may not be present. A preferred active agent is a chloride salt of TAT-NR2B9c. A preferred buffer is histidine. A preferred bulking agent is trehalose. Trehalose also serves as a cryo and lyo-preserved. An exemplary prelyophilized formulation comprises the active agent (e.g., chloride salt of TAT-NR2B9c), histidine (10-100 mM, 15-100 mM 15-80 mM, 40-60 mM or 15-60 mM, for example, 20 mM or optionally 50 mM, or 20-50mM)) and trehalose (50-200 mM, preferably 80-160 mM, 100-140 mM, more preferably 120 mM). The pH is 5.5 to 7.5, more preferably, 6-7, more preferably 6.5. The concentration of active agent (e.g., chloride salt of TAT-NR2B9c) is 20-200 mg/ml, preferably 50-150 mg/ml, more preferably 70-120 mg/ml or 90 mg/ml. Thus, an exemplary prelyophilized formulation is 20 mM histidine, 120 mM trehalose, and 90 mg/ml chloride salt of TAT-NR2B9c. Optionally an acetylation scavenger, such as lysine can be included, as described in co-pending application 057769-446850, to further reduce any residual acetate or trifluoroacetate in the formulation

[0037] After lyophilization, lyophilized formulations have a low-water content, preferably from about 0%-5% water, more preferably below 2.5% water by weight. Lyophilized formulations can be stored in a freezer (e.g., -20 or -70° C), in a refrigerator (0-4° C) or at room temperature (20-25° C).

CLAIMS

1. A chloride salt of a peptide which is TAT-NR2B9c (SEQ ID NO:6) or differs from TAT-NR2B9c by up to 5 amino acid substitutions, insertions or deletions, wherein greater than 99% of anions in the salt are chloride.
2. The chloride salt of claim 1, which is TAT-NR2B9c.
3. The chloride salt of claim 1, prepared by exchanging trifluoroacetate for chloride in a trifluoroacetate salt of TAT-NR2B9c.
4. The chloride salt of claim 1, prepared by exchanging trifluoroacetate for acetate and then acetate for chloride starting from a trifluoroacetate salt of TAT-NR2B9c.
5. A prelyophilized formulation comprising the chloride salt of claim 1, a buffer and a sugar.
6. The prelyophilized formulation of claim 5, wherein the chloride salt is a chloride salt of TAT-NR2B9c.
7. The prelyophilized formulation of claim 6, wherein the buffer is histidine and the sugar is trehalose and the pH is 6-7.
8. The prelyophilized formulation of claim 6, wherein acetate and trifluoroacetate each comprise less than 0.1% by weight of anions in the formulation.
9. The prelyophilized formulation of claim 7, wherein the chloride salt of the peptide is at a concentration of 70-120 mg/ml, the histidine is at a concentration of 15-100 mM, and the trehalose is at a concentration of 80-160 mM.
10. The prelyophilized formulation of claim 9, wherein the chloride salt of the peptide is at a concentration of 70-120 mg/ml, the histidine is at a concentration of 20-100 mM, and the trehalose is at a concentration of 100-140 mM.
11. The prelyophilized formulation of claim 6, wherein the Tat-NR2B9c is at a concentration of 70-120 mg/ml, the concentration of histidine 20-50 mM, and the concentration

of trehalose is 100-140 mM.

12. The prelyophilized formulation of claim 6, wherein the concentration of histidine is 20 mM and the concentration of trehalose is 100-200 mM, and the concentration of TAT-NR2B9c is 90 mg/ml.

13. A lyophilized formulation prepared by lyophilizing the prelyophilized formulation of claim 5.

14. The lyophilized formulation of claim 13, wherein acetate and trifluoroacetate each comprise less than 0.1% by weight of anions in the formulation.

15. A reconstituted formulation prepared by combining the lyophilized formulation of claim 13 with an aqueous solution.

16. The reconstituted formulation of claim 15, wherein the aqueous solution is water or normal saline.

17. The reconstituted formulation of claim 15, wherein the volume of the reconstituted formulation is 3-6 times the volume of the prelyophilized formulation.

18. A reconstituted formulation comprising a chloride salt of TAT-NR2B9c at a concentration of 15-25 mg/ml, a buffer and a sugar.

19. The reconstituted formulation of claim 18, wherein the buffer is histidine at a concentration of 4-20 mM and the sugar is trehalose at a concentration of 20-30 mM and the pH is 6-7.

20. The reconstituted formulation of claim 19 wherein acetate and trifluoroacetate each comprise less than 1% by weight of anions in the formulation.

21. The reconstituted formulation of claim 19, wherein acetate and trifluoroacetate each comprise less than 0.1% by weight of anions in the formulation.

22. A method of preparing a formulation, comprising storing a lyophilized formulation according to claim 13 for at least a week at a

temperature of at least 20°C; and

reconstituting the lyophilized formulation.

23. The method of claim 22, wherein the lyophilized formulation is reconstituted in water.

24. The method of claim 22, wherein the lyophilized formulation is reconstituted in saline.

25. The method of claim 22, further comprising administering the reconstituted formulation, optionally after further dilution in normal saline, to a patient.

26. The method of claim 25, wherein the lyophilized formulation is stored for at least a year.

27. The method of claim 26, wherein the storage is at ambient temperature.

28. The method of claim 27, wherein the storage includes periods in which the temperature exceeds 37°C.

29. The method of claim 25, wherein the patient has stroke or traumatic injury to the CNS.

30. The method of claim 25, wherein the lyophilized formulation is stored in an ambulance.

31. The method of claim 25, wherein the patient has a subarachnoid hemorrhage.

32. The method of claim 25, wherein the patient is undergoing endovascular repair for an aneurysm.

33. The chloride salt of claim 1, wherein greater than 99.5% of anions in the salt are chloride.

34. The prelyophilized formulation of claim 12, wherein the concentration of trehalose is 120 mM.