peptide ligands interact with the molecular backbone of Vancomycin and related glycopeptide antibiotics in multiple places, while single amino acid ligands such as N-acetyl-D-Alanine interact in a more limited fashion. See, e.g., Brown JP et al. (1975), *Mol. Pharmacol.* 11:126-132; Harris CM et al. (1984), *J. Antibiotics* 38(1): 51-57; Williams DH et al. (1993), *Proc. Nat. Acad. Sci.* US 90:1172-1178; Pearce CM et al. (1995), *J. Chem. Sci.* Perkins Trans. 2: 159-162; and Rao J et al. (1999), *Chem. & Biol.* 6: 353-359. Harris CM et al. suggest that the relative structural rigidity conveyed to the Vancomycin molecule on binding with di- and tri-peptides in solution blocked rearrangement of the Vancomycin backbone asparagine to isoaspartate via a cyclic imide intermediate. This is consistent with the observation of the inventors in US4670258 discussed above. However, although single amino acid ligands such as N-acetyl-D-Alanine may be involved in glycopeptide antibiotic dimerization in solution under certain conditions, it is not clear that such ligands confer similar structural rigidity in a complex with antibiotics such as Vancomycin as do the di- and tri-peptide ligands. Moreover, these studies did not investigate or discuss the long-term stability of Vancomycin and related glycopeptide antibiotics in solutions for pharmaceutical use.

Raverdy et al (*J Antimicrob Chemother* 2013; 68: 1179–1182), observed the stability of an intravenous solution of 10 g/L Vancomycin in 5% glucose for up to 48 hours under conditions that simulated delivery of the solution to a patient, and for up to 72 hours at 50 degrees Celsius. The study also examined the solution's compatibility with various substances co-administered through a Y-connector, for a contact time of one hour at room temperature. The authors concluded that, under the observed conditions and times, the Vancomycin was stable and that N-acetyl-Cysteine (used as an antioxidant in cases of Paracetamol intoxication) and amino acid solutions (used for parenteral nutrition) did not cause alteration of Vancomycin when co-administered. However, the conditions and components necessary for long-term stability of Vancomycin solutions were not investigated or discussed.

Thus, there remains a need for solutions of Vancomycin and related glycopeptides which possess long-term stability under conditions of normal use and storage, and which remain suitable for administration to a subject throughout their stability period.

Summary

In one aspect, there is provided a composition comprising a glycopeptide antibiotic and an excipient selected from N-acetyl-D-Alanine or N-acetyl-Glycine for use as a medicament.

In another aspect, there is provided a pharmaceutical composition comprising a glycopeptide antibiotic; and an excipient selected from N-acetyl-D-Alanine or N-acetyl-Glycine.

In a further aspect, there is provided a method for stabilizing a glycopeptide antibiotic in a pharmaceutical solution by mixing N-acetyl-D-Alanine or N-acetyl Glycine and the glycopeptide antibiotic.

The present disclosure provides stabilized pharmaceutical compositions comprising glycopeptide antibiotics. In some exmples, present disclosure provides stabilized pharmaceutical compositions comprising Vancomycin.

The present disclosure provides glycopeptide antibiotic compositions comprising an N-acetyl-D-amino acid or N-acetyl-Glycine.

The present disclosure provides glycopeptide antibiotic compositions comprising an N-acetyl-D-amino acid or N-acetyl-Glycine for use as a medicament.

The present disclosure provides glycopeptide antibiotic compositions comprising an N-acetyl-D-amino acid or N-acetyl-Glycine for use in treatment of bacterial infections.

The present disclosure provides glycopeptide antibiotic compositions comprising N-acetyl-D-Alanine or N-acetyl-Glycine.

The present disclosure provides glycopeptide antibiotic compositions comprising N-acetyl-D-Alanine or N-acetyl-Glycine for use as a medicament.

The present disclosure provides glycopeptide antibiotic compositions comprising N-acetyl-D-Alanine or N-acetyl-Glycine for use in treatment of bacterial infections.

In one example of the present disclosure, the compositions are aqueous.

In one example of the present disclosure, the compositions are aqueous and have a pH of about 2-7.

In one example of the present disclosure, the compositions are aqueous and have a pH of about 3-6.

In one examples of the present disclosure, the compositions are aqueous and have a pH of about 4.0-5.5.

In one example of the present disclosure, the compositions are aqueous and have a pH of about 4.5-5.5.

In one example of the present disclosure, the compositions further comprise an amino acid and/or an organic solvent.

In one example of the present disclosure, the compositions further comprise an amino acid selected from Glycine, Alanine, Serine, Leucine, Valine, Lysine, Arginine and Ornithine.

In one example of the present disclosure, the compositions further comprise an amino acid selected from D-Alanine, D-Serine, D-Leucine, D-Valine, L-Lysine, D-Lysine, L-Ornithine, D-Ornithine or L-Arginine.

In one example of the present disclosure, the compositions further comprise an amino acid selected from D-Serine, D-Leucine, D-Valine, L-Lysine, D-Lysine, L-Ornithine, D-Ornithine or L-Arginine.

The compositions according to the present disclosure are suitable for storage in liquid state, thus providing vials, syringes and "ready to use" IV containers, as are known in the art, comprising the stabilized Vancomycin compositions. When administering these to patients, there is no need for the step of reconstituting a lyophilized Vancomycin powder; however, the content of vials and syringes could be further diluted to target concentration prior to administration. Suitable diluents for solutions of the invention include any known diluent acceptable for pharmaceutical use (e.g., intravenous administration); for example, water, physiological saline, 5% dextrose solution, lactated Ringer's solution or combinations thereof.

The present disclosure further provides a method for stabilizing glycopeptide antibiotics which involves addition of N-acetyl-D-amino acids to a solution comprising a glycopeptide antibiotic or addition of a glycopeptide antibiotic to a solution comprising N-acetyl-D-amino acids.

In one example, at least one additional amino acid is also added and/or at least one pharmaceutically acceptable organic solvent is added.

The present disclosure provides a method for stabilizing a glycopeptide antibiotic which involves addition of N-acetyl-D-Alanine to a solution comprising a glycopeptide antibiotic or addition of a glycopeptide antibiotic to a solution comprising N-acetyl-D-Alanine.

In one example, at least one additional amino acid is also added and/or at least one pharmaceutically acceptable organic solvent is added.

The present disclosure provides solutions comprising about 0.1-1% w/V of Vancomycin and N-acetyl-D-Alanine, wherein the solutions have a pH of about 4-6.

In one example, the solutions further comprise an amino acid selected from D-Alanine, D-Serine, D-Leucine, D-Valine, L-Lysine, D-Lysine, L-Ornithine, D-Ornithine or L-Arginine.

In another example, the solutions further comprise L-Lysine.

In another example, the solutions further comprise L-Lysine and have a pH of about 4.5-5.5.

In another example, the solutions further comprise L-Lysine and have a pH of about 4.5-5.5, wherein the molar ratio of glycopeptide antibiotic to L-Lysine is about 1:5-1:30.

In another example, the solutions further comprise L-Lysine and have a pH of about 4.5-5.5, wherein the molar ratio of glycopeptide antibiotic to N-acetyl-D-Alanine is about 1:5-1:40 and wherein the molar ratio of glycopeptide antibiotic to L- Lysine is about 1:5-1:30.

The present disclosure provides solutions comprising about 3-10% w/V glycopeptide antibiotic and N-acetyl-D-Alanine, wherein the solutions have a pH of about 4-6.

The present disclosure provides solutions comprising about 0.1-1% w/V glycopeptide antibiotic and N-acetyl-D-Alanine, wherein the solutions have a pH of about 4-6.

The present disclosure provides solutions comprising about 1-10% w/V glycopeptide antibiotic and N-acetyl-D-Alanine, wherein the solutions have a pH of about 4-6.

In one example, the solutions further comprise an amino acid selected from D-Alanine, D-Serine, D-Leucine, D-Valine, L-Lysine, D-Lysine, L-Ornithine, D-Ornithine or L-Arginine.

In another example, the solutions further comprise L-Lysine.

In another example, the solutions further comprise L-Lysine and have a pH of about 4.5-5.5.

In another example, the solutions further comprise L-Lysine and have a pH of about 4.5-5.5, wherein the molar ratio of glycopeptide antibiotic to L-Lysine is about 1:0.5-1:4.

In another example, the solutions further comprise L-Lysine and have a pH of about 4.5-5.5, wherein the molar ratio of glycopeptide antibiotic to N-acetyl-D-Alanine is about 1:1-1:4 and wherein the molar ratio of glycopeptide antibiotic to L-Lysine is about 1:0.5-1:4.

The present disclosure provides aqueous solutions comprising about 0.5% w/V of glycopeptide antibiotic and L-Lysine and N-acetyl-D-Alanine in a molar ratio of about 1:20:30, wherein the solutions have a pH of about 4.5-5.5.

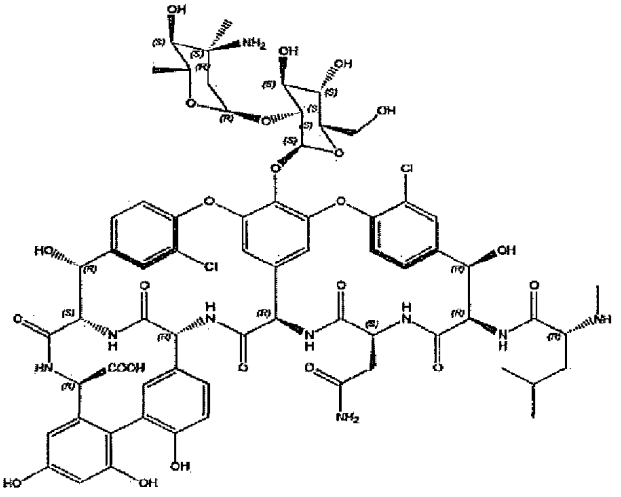
The present disclosure provides aqueous solutions comprising about 5% w/V of glycopeptide antibiotic and L-Lysine and N-acetyl-D-Alanine in a molar ratio of about 1:2:2, wherein the solutions have a pH of about 4.5-5.5.

Brief Description of the Drawing

Figure 1 is a representation of the molecular structures of Vancomycin, Teicoplanin, Telavancin, Dalbavancin and Oritavancin as disclosed by Kang and Park, *Journal of Bacteriology and Virology* 2015 vol. 45 no. 2 pages 67-78.

Detailed Description

Vancomycin is a tricyclic glycopeptide antibiotic. Its structure is represented in Formula 1. Its purity in the formulation can be assessed by the content of Vancomycin B.



Formula 1.

"Vancomycin" as used herein means the compound represented in Formula 1 and also pharmaceutically acceptable salts thereof, for example Vancomycin Hydrochloride.

CLAIMS

1. **A composition comprising a glycopeptide antibiotic and an excipient selected from N-acetyl-D-Alanine or N-acetyl-Glycine for use as a medicament.**

2. A liquid composition according to claim 1.

3. An aqueous composition according to claim 2.

4. A composition according to claim 3 having a pH of about 3-6 and further comprising an amino acid.

5. A composition according to claim 4 wherein the concentration of the glycopeptide antibiotic is about 0.1-20% w/V.

6. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 0.1-1% w/V; and the amino acid is selected from Glycine, Alanine, Serine, Leucine, Valine, Lysine, Arginine or Ornithine; and the excipient is N-acetyl-D-Alanine.

7. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 0.1-1% w/V; and the amino acid is selected from Lysine, Arginine or Ornithine; and the excipient is N-acetyl-D-Alanine.

8. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 0.1-1% w/V; and the amino acid is selected from Glycine, Alanine, Serine, Leucine, Valine, Lysine, Arginine or Ornithine; and the excipient is N-acetyl-D-Alanine, wherein the glycopeptide antibiotic , amino acid and N-acetyl-D-Alanine are present in a molar ratio of about 1:5:5 to 1:40:40.

9. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 0.1-1% w/V; and the amino acid is selected from L-Lysine, D-Lysine, L-Ornithine, D-Ornithine or L-Arginine; and the excipient is N-acetyl-D-Alanine, wherein the glycopeptide antibiotic , amino acid and N-acetyl-D-Alanine are present in a molar ratio of about 1:5:5 to 1:40:40.

10. A composition according to claim 1, wherein the glycopeptide antibiotic is Vancomycin, Teicoplanin, Telavancin, Dalbavancin or Oritavancin.

11. A composition according to claim 10, wherein the glycopeptide antibiotic is Vancomycin.

12. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 0.5% w/V; and the amino acid is L-Lysine;

and the excipient is N-acetyl-D-Alanine, wherein the glycopeptide antibiotic, amino acid and N-acetyl-D-Alanine are present in a molar ratio of about 1:20:30; and wherein the composition has a pH of about 4.5-5.5.

13. A composition according to claim 5 wherein the glycopeptide antibiotic is Vancomycin.

14. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 1-10% w/V; and the amino acid is selected from Glycine, Alanine, Serine, Leucine, Valine, Lysine, Arginine or Ornithine; and the excipient is N-acetyl-D-Alanine.

15. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 1-10% w/V; and the amino acid is selected from Lysine, Arginine or Ornithine; and the excipient is N-acetyl-D-Alanine.

16. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 1-10% w/V; and the amino acid is selected from Glycine, Alanine, Serine, Leucine, Valine, Lysine, Arginine or Ornithine; and the excipient is N-acetyl-D-Alanine; and wherein the glycopeptide antibiotic, amino acid and N-acetyl-D-Alanine are present in a molar ratio of about 1:1:1 to 1:10:10.

17. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 1-10% w/V; and the amino acid is selected from L-Lysine, D-Lysine, L-Ornithine, D-Ornithine or L-Arginine; and the excipient is N-acetyl-D-Alanine; and wherein the glycopeptide antibiotic, amino acid and N-acetyl-D-Alanine are present in a molar ratio of about 1:1:1 to 1:10:10.

18. A composition according to claim 5 wherein the concentration of the glycopeptide antibiotic is about 5% w/V; and the amino acid is L-Lysine; and the excipient is N-acetyl-D-Alanine, and wherein the glycopeptide antibiotic, amino acid and N-acetyl-D-Alanine are present in a molar ratio of about 1:2:2; and wherein the compositions have a pH of about 4.5-5.5.

19. A composition according to claim 18 wherein the glycopeptide antibiotic is Vancomycin.

20. A pharmaceutical composition comprising a glycopeptide antibiotic; and an excipient selected from N-acetyl-D-Alanine or N-acetyl-Glycine.

21. The pharmaceutical composition of claim 20, wherein the pharmaceutical composition is prepared for parenteral administration.

22. The pharmaceutical composition of claim 20, further comprising an amino acid.

23. A liquid pharmaceutical composition according to claim 20.

24. An aqueous pharmaceutical composition according to claim 23.

25. A pharmaceutical composition according to claim 24 wherein the amino acid is selected from Glycine, Alanine, Serine, Leucine, Valine, Lysine, Arginine or Ornithine.

26. A pharmaceutical composition according to claim 24 wherein the amino acid is selected from D-Alanine, D-Serine, D-Leucine, D-Valine, L-Lysine, D-Lysine, L-Ornithine, D-Ornithine or L-Arginine.

27. A pharmaceutical composition according to claim 26 wherein the amino acid is selected from L-Lysine, D-Lysine, L-Ornithine, D-Ornithine or L-Arginine.

28. A pharmaceutical composition according to claim 27 wherein the amino acid is selected from L-Lysine or D-Lysine.

29. A pharmaceutical composition according to any of claims 24-28 having a pH of about 3-6.

30. A pharmaceutical composition according to any of claims 24-28 wherein the concentration of the glycopeptide antibiotic is 0.1-1% w/V; and wherein N-acetyl-D-Alanine is present in a suitable molar ratio.

31. A pharmaceutical composition according to any of claims 24-28 wherein the concentration of the glycopeptide antibiotic is 1-10% w/V; and wherein N-acetyl-D-Alanine is present in a suitable molar ratio.

32. A pharmaceutical composition according to claim 20, wherein the glycopeptide antibiotic is Vancomycin, Teicoplanin, Telavancin, Dalbavancin or Oritavancin.

33. A composition according to claim 32, wherein the glycopeptide antibiotic is Vancomycin.

34. A pharmaceutical composition according to claim 24 wherein the concentration of the glycopeptide antibiotic is about 0.5% w/V; and the amino acid is L-Lysine; and the excipient is N-acetyl-D-Alanine; and wherein the glycopeptide antibiotic, amino acid and N-acetyl-D-Alanine are present in a molar ratio of about 1:20:30; and wherein the composition has a pH of about 4.5-5.5.

35. A pharmaceutical composition according to claim 24 wherein the concentration of the glycopeptide antibiotic is about 5% w/V and the amino acid is L-Lysine and the excipient is N-acetyl-D-Alanine; and wherein the glycopeptide antibiotic, amino acid and N-acetyl-D-Alanine are present in a molar ratio of about 1:2:2; and wherein the composition has a pH of about 4.5-5.5.

36. A pharmaceutical composition according to either of claims 34 or 35, wherein the glycopeptide antibiotic is Vancomycin.

37. A method for stabilizing a glycopeptide antibiotic in a pharmaceutical solution by mixing N-acetyl-D-Alanine or N-acetyl Glycine and the glycopeptide antibiotic.

38. The method of claim 37, wherein N-acetyl-D-Alanine or N-acetyl Glycine is added to a solution comprising the glycopeptide antibiotic or the glycopeptide antibiotic is added to a solution comprising N-acetyl-D-Alanine or N-acetyl-Glycine.

39. The method of claim 37, wherein N-acetyl-D-Alanine is added to a solution comprising the glycopeptide antibiotic or the glycopeptide antibiotic is added to a solution comprising N-acetyl-D-Alanine.

40. The method of either claims 38 or 39, wherein the glycopeptide antibiotic is Vancomycin.

41. The method of claim 37, wherein the pharmaceutical solution is prepared for parenteral administration.