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, wherein the composition is a liquid composition.

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, wherein the composition is in liquid form.

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.

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, wherein the composition is a liquid composition.

2. A composition according to claim 1, wherein the composition is an aqueous composition.

3. A composition according to claim 2 having a pH of about 3-6 and further comprising an amino acid.

4. A composition according to claim 3 wherein the concentration of the glycopeptide antibiotic is about 0.1-20% w/V.

5. A composition according to claim 4 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.

6. A composition according to claim 4 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.

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

8. A composition according to claim 4 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.

9. A composition according to claim 4 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.

10. A composition according to claim 4 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.

11. A pharmaceutical composition comprising a glycopeptide antibiotic; and an excipient selected from N-acetyl-D-Alanine or N-acetyl-Glycine, wherein the composition is in liquid form.

12. The pharmaceutical composition of claim 11, wherein the pharmaceutical composition is prepared for parenteral administration.

13. An pharmaceutical composition according to claim 12, wherein the composition is an aqueous composition.

14. The pharmaceutical composition of claim 12, further comprising an amino acid.

15. A pharmaceutical composition according to claim 13 or 14 wherein the amino acid is selected from Glycine, Alanine, Serine, Leucine, Valine, Lysine, Arginine or Ornithine.

16. A pharmaceutical composition according to claim 13 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.

17. A pharmaceutical composition according to any of claims 13-16 having a pH of about 3-6.

18. The pharmaceutical composition according to claim 14, wherein the molar ratio of an amino acid to glycopeptide antibiotic is about 0.5:1 to 40:1.

19. A pharmaceutical composition according to claim 11, wherein the glycopeptide antibiotic is Vancomycin, Teicoplanin, Telavancin, Dalbavancin or Oritavancin.

20. The pharmaceutical composition according to any of the claims 15-18, further comprising organic solvent selected from ethanol or polyethylene glycol, wherein the concentration of the organic solvent is 50% V/V or less.

21. A pharmaceutical composition according to claim 13 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.

22. A pharmaceutical composition according to claim 13, wherein the pharmaceutical solution is stable for at least 4 weeks at 25 degrees Celsius, as demonstrated by determining the amount of the vancomycin remaining in the pharmaceutical solution after at least 4 weeks at 25 degrees Celsius, and wherein

the amount of the vancomycin remaining in the pharmaceutical solution is between 85% and 100%.

23. 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.

24. The method of claim 23, 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.

25. The method of claim 23, 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.

26. The method of either claims 24 or 25, wherein the glycopeptide antibiotic is Vancomycin.

27. The method of claim 23, wherein the pharmaceutical solution is prepared for parenteral administration.