In *Journal of Liquid Chromatography & Related Technologies, 2012, 35:2845–2859,* article "Effect of sulfobutyl ether beta-cyclodextrin modifier on selectivity of reversed phase HPLC separations" by Ngim et al., discloses a HPLC method involving a sulfobutylether β-cyclodextrin which improved main peak resolution or altered impurity profiles of Vancomycin. The mobile phase contained acetonitrile.

In Ngim et al.: "Characterization and resolution of reversed phase HPLC chromatography failure attributed to sulfobutylether-β-cyclodextrin in a pharmaceutical sample preparation", published in *Journal of Pharmaceutical and Biomedical Analysis, 49 (2009) 660–669,* reversed phase HPLC method failure during analysis of an unknown Vancomycin derivative is disclosed.

US7635773 discloses high-purity sulfoalkyl ether cyclodextrins.

Despite all the effort, none of those listed publications were able to provide pharmaceutical formulations of glycopeptides, especially Vancomycin, in liquid form that show satisfying stability at room temperature for prolonged period of time.

Accordingly, there remains a need for liquid compositions 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, the present disclosure provides a liquid pharmaceutical composition comprising a glycopeptide antibiotic and sulfobutylether-betacyclodextrin, wherein the pharmaceutical composition is stable for at least about four weeks (1 month) at 25 degrees Celsius in a closed container.

The glycopeptides may be selected from Vancomycin, Telavancin, Oritavancin, Teicoplanin and Dalbavancin.

In one embodiment the glycopeptide is Vancomycin.

The liquid pharmaceutical compositions according to the disclosure show chemical and physical stability at room temperature. Accordingly, they require no additional steps of preparation, such as, e.g. reconstitution of a lyophilized powder or thawing.

By allowing the use of the composition right off the shelf without any additional preparation, potential contamination problems and dosage errors are prevented.

Furthermore, the liquid pharmaceutical compositions do not require special storage conditions, such as, e.g. freezing or storage in a refrigerator.

The present disclosure also provides methods for treatment of bacterial infections in a subject, wherein a liquid pharmaceutical composition according to the disclosure is administered to the subject.

The disclosure further provides a method for stabilizing glycopeptide antibiotics by mixing the glycopeptide antibiotic with sulfobutylether-beta cyclodextrin in a ratio of glycopeptide antibiotic to sulfobutylether-beta cyclodextrin at which the pharmaceutical solution is stable for at least about four weeks (1 month) at 25 degrees Celsius in a closed container.

In another aspect, there is provided a method for stabilizing a glycopeptide antibiotic in a liquid pharmaceutical solution as defined herein comprising mixing sulfobutylether-beta cyclodextrin and the glycopeptide antibiotic in a ratio of glycopeptide antibiotic to sulfobutylether-beta cyclodextrin at which the pharmaceutical solution is stable for at least about four weeks at 25 degrees Celsius in a closed container.

The disclosure also relates to a method of manufacturing liquid pharmaceutical solutions comprising the steps of mixing a glycopeptide antibiotic and sulfobutylether-betacyclodextrin in a ratio of glycopeptide antibiotic to sulfobutylether-beta cyclodextrin at which the pharmaceutical solutions are stable for at least about four weeks (1 month) at 25 degrees Celsius in a closed container.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description and examples. It should be understood, however, that the detailed description and the examples, while indicating specific embodiments of the disclosure, are given by way of illustration only and are not intended as a definition of the limits of the disclosure.

Claims

1. A liquid pharmaceutical composition comprising a glycopeptide antibiotic and sulfobutylether-betacyclodextrin, wherein the pharmaceutical composition is stable for at least about four weeks at 25°C in a closed container.

2. The pharmaceutical composition of claim 1, wherein the glycopeptide antibiotic is Vancomycin.

3. The pharmaceutical composition of any of claims 1-2, having a pH of about 2.0 to about 6.0.

4. The pharmaceutical composition of any of claims 1-3, wherein the concentration of the glycopeptide antibiotic is between about 0.1% w/V and 15% w/V.

5. The pharmaceutical composition of claim 4, wherein the concentration of the glycopeptide antibiotic is about 0.5 w/V, 5% w/V or 10% w/V.

6. The pharmaceutical composition of any one of claims 1-5, wherein the glycopeptide antibiotic and sulfobutylether-betacyclodextrin are present in a ratio of about 1:0.5 to 1:40 of glycopeptide antibiotic:sulfobutylether-betacyclodextrin.

7. The pharmaceutical composition according to any one of claims 1-6, further comprising an organic solvent.

8. The pharmaceutical composition of claim 7, wherein the organic solvent comprises ethanol, propylene glycol or polyethylene glycol, or combinations thereof.

9. The pharmaceutical composition of any one of claims 1-8, further comprising an excipient selected from N-acetyl-D-Alanine or N-acetyl-Glycine.

10. The pharmaceutical composition of claim 9, wherein the glycopeptide antibiotic, sulfobutylether-betacyclodextrin and N-acetyl-D-Alanine are present in a ratio of about 1:2.2:2 glycopeptide antibiotic:sulfobutylether-betacyclodextrin:N-acetyl-D-Alanine.

11. The pharmaceutical composition of any one of claims 1-9, further comprising an amino acid.

12. A pharmaceutical composition according to claim 11, 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.

13. The pharmaceutical composition of claim 11, wherein the concentration of the glycopeptide antibiotic is about 0.5% w/V, the glycopeptide antibiotic, sulfobutylether-betacyclodextrin, N-acetyl-D-Alanine and amino acid are present in a molar ratio of about 1:0.67:30:20 and the composition has a pH of about 4.5-5.5.

14. The pharmaceutical composition of claim 11, wherein the concentration of the glycopeptide antibiotic is about 5% w/V, the glycopeptide antibiotic, sulfobutylether-betacyclodextrin, N-acetyl-D-Alanine and amino acid are present in a molar ratio of about 1:0.067:2:2 and the composition has a pH of about 4.5-5.5.

15. The pharmaceutical composition of claim 11, wherein the concentration of the glycopeptide antibiotic is about 10% w/V, the glycopeptide antibiotic, sulfobutylether-betacyclodextrin, N-acetyl-D-Alanine and amino acid are present in

a molar ratio of about 1:2:1:1, and the composition further comprises 9.6% v/v ethanol and has a pH of about 4.5-5.5.

16. The pharmaceutical composition of any of claim 1-15, wherein the pharmaceutical composition is prepared for parenteral administration.

17. A method for stabilizing a glycopeptide antibiotic in a liquid pharmaceutical solution according to any of claim 1-16 comprising mixing sulfobutylether-beta cyclodextrin and the glycopeptide antibiotic in a ratio of glycopeptide antibiotic to sulfobutylether-beta cyclodextrin at which the pharmaceutical solution is stable for at least about four weeks at 25 degrees Celsius in a closed container.