resistance and no cross-resistance with existing therapeutic antibiotics, as a consequence of its mechanism of action. However, a stable topical pexiganan composition has been very difficult to formulate and is not presently available.

Peptides are often challenging to formulate as they exhibit chemical instability, adopt multiple conformations, tend to self-associate and also exhibit complex physical instabilities, especially in topical form. Both chemical and physical stability are critical to an effective and commercial pharmaceutical formulation. An unstable formulation results in loss of potency and poor quality and patient compliance. Topical formulations, especially, must remain stable in the container while stored long term and then when applied to the skin. Thus, there remains a need for a dosage form for the topical administration of pexiganan, which provides effective treatment of wound infection, and which remains chemically and physically stable over a long storage term.

SUMMARY

The present ~~invention~~ disclosure overcomes the problems outlined above and advances the art by providing stable pexiganan formulations for topical administration. The formulations of the present ~~invention~~ disclosure have both increased chemical stability and physical stability over the long term.

As such, in one ~~embodiment~~aspect, the present ~~invention~~ disclosure provides a topical formulation comprising pexiganan or an acid addition salt thereof comprising a first hydrophilic surfactant having an HLB value between about 12 and about 17 and a second hydrophobic surfactant having an HLB value between about 3.5 and about 5.5 , wherein the first hydrophilic and second hydrophobic surfactants comprise from about 1.5 to about 5.0 % w/w of the formulation and the weight ratio of the first to second surfactants is such that the blended HLB is between 12.5 and about 14.5.

Preferably, the HLB value of the first hydrophilic surfactant is between about 13 and about 16, and more preferably, the HLB value of the first hydrophilic surfactant is 14.9. Preferably, the HLB value of the second hydrophobic surfactant is between about 3.5 and about 5.5, and more preferably, the HLB value of the second hydrophilic surfactant is 4.7.

Preferably, the first hydrophilic and second hydrophobic surfactants comprise from about 2 % w/w to about 4.5 % w/w of the formulation. More preferably, the first hydrophilic and second hydrophobic surfactants comprise about 3.5 % w/w of the formulation.

Preferably, the blended HLB of the first hydrophilic and second hydrophobic surfactants is between about 12.5 and about 14.5. More preferably, the blended HLB of the first hydrophilic surfactants and second hydrophobic surfactants is 13.6. Also preferably, the blended HLB of the first ~~hydrophobic~~ hydrophilic surfactant and second hydrophobic surfactant is 14.4.

Preferably, the first hydrophilic surfactant is Tween 60 and the second hydrophobic surfactant is Span 60.

In another ~~embodiment~~aspect, the stable topical formulation may comprise 1.05 (% w/w) pexiganan acetate; 20.0 (% w/w) propylene glycol; 0.1 (% w/w) EDTA; 7.5 (% w/w) stearyl alcohol; 2.0 (% w/w) cetyl alcohol; 1.0 (% w/w) isopropyl myristate; 0.1 (% w/w) BHT; 0.43 (% w/w) Span 60; 3.07 (% w/w) Tween 60; 0.1 (% w/w) Tween 80 and (q.s.a.d.) sodium acetate buffer.

In another ~~embodiment~~aspect, the stable topical formulation may comprise 1.05 (% w/w) pexiganan acetate; 20.0 (% w/w) propylene glycol; 0.1 (% w/w) EDTA; 6.0 (% w/w) stearyl alcohol; 2.0 (% w/w) cetyl alcohol; 3.0 (% w/w) isopropyl myristate; 0.1 (% w/w) BHT; 0.17 (% w/w) Span 60; 3.33 (% w/w) Tween 60; 0.1 (% w/w) Tween 80 and (q.s.a.d.) sodium acetate buffer.

In a further ~~embodiment~~aspect, the present ~~invention~~ disclosure provides a use of an effective amount of a topical formulation of claim 1 in the manufacture of a medicament for treating a skin or wound infection in a patient in need thereof. Also provided is ~~provides~~ a method of treating a skin or wound infection comprising topically applying to a patient in need thereof at the site of infection an effective amount of the formulations of the present invention.

DETAILED DESCRIPTION

It has now been discovered that topical formulations can be prepared comprising pexiganan which are chemically and physically stable. Additional aspects of the present invention will become more apparent from the detailed description of the following embodiments.

For purposes of the present disclosure, the following terms have the following meanings:

The term "active ingredient" refers to an ingredient having a therapeutic or cosmetic activity.

The term "topical application" refers to an application to the skin, including skin wounds, hair, ears, mucous membranes, rectal application, nasal application, as well as dental application within the oral cavity.

The first hydrophilic and second hydrophobic surfactants together may comprise from about 1.5 to about 5.0 % w/w of the formulation. Preferably, the first hydrophilic and second hydrophobic surfactants comprise from about 2 to about 4.5 % w/w of the formulation. More preferably, the first hydrophilic and second hydrophobic surfactants comprise about 3.5 % w/w of the formulation. When the first a hydrophilic and the second emulsifier are present together, the blended HLB of the two emulsifiers may be measured. Blended HLB is calculated by taking the weighted average of the individual HLB values, as weighted by the percentage of the formulation comprised of the individual emulsifier. Preferably the blended HLB of the first ~~hydrophobic~~ hydrophilic emulsifier and second hydrophobic emulsifier is between about 12.5 and about 14.5. Also preferably, the blended HLB of the first hydrophilic ~~hydrophobic~~ surfactant and second hydrophobic surfactant is 14.4.

Further emulsifiers, such as a third or fourth, or more, emulsifiers, may be used in addition to the first emulsifier and second emulsifier.

The present formulations may include chelating agents. Preferred chelating agents include, but are not limited to for example, ethylenediaminetetraacetic acid (EDTA), disodium edetate and EDTA derivatives, citric acid, and mixtures thereof.

The present formulations may include stiffening agents, as used to increase the viscosity and/or increase consistency. Preferred stiffening agents may include, but are not limited to, stearyl alcohol, cetyl alcohol, waxes, ceteareth-20, ceteareth-30, cetearyl alcohol, ceteth 20, cetostearyl alcohol, cetyl alcohol, cetyl stearyl alcohol, and mixtures thereof.

The present formulations may include solvents. Preferred solvents include, but are not limited to, propylene glycol, water, isopropyl alcohol, liquid petrolatum, ether, petroleum ether, alcohols (*e.g.*, ethanol and higher alcohols), silicones, aromatics (*e.g.*, toluene), alkanes (*e.g.*, pentane, hexane and heptane), ketones (*e.g.*, acetone and methyl ethyl ketone), chlorinated hydrocarbons (*e.g.*, chloroform, carbon tetrachloride, methylene chloride and ethylene dichloride), acetates (*e.g.,* ethyl acetate), esters and oils (*e.g.*, isopropyl myristate, diisopropyl adipate and mineral oil) and mixtures thereof. The solvent may also have antimicrobial properties.

The present formulations may include preservatives. Preferred preservatives may include, but are not limited to, phenoxyethanol, parabens (such as methylparaben and propylparaben), propylene glycols, sorbates, urea derivatives (such as diazolindinyl urea), and mixtures thereof.

13. ~~A method of treating a skin or wound infection comprising topically applying to a patient in need thereof at the site of infection~~ Use of an effective amount of a topical formulation of claim 1 in the manufacture of a medicament for treating a skin or wound infection in a patient in need thereof.