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**TWO PHASE BIOACTIVE FORMULATIONS
OF BIS-QUATERNARY PYRIDINIUM OXIME
SULFONATE SALTS**

GOVERNMENT RIGHTS CLAUSE

This invention was made with United States Government support under Contract No. W9113M-05-C-0199 awarded by the United States Army. The Government has certain rights in this invention.

FIELD OF THE INVENTION

The present invention relates to two-phase systems of a bioactive ingredient in particle form that has limited or no solubility in a liquid medium, which provides stability to the active ingredient that is similar to the active ingredient when in the solid state. The active ingredient may be a bis-quaternary pyridinium-aldoxime salt which may be used for treatment of exposure to cholinesterase inhibitors, such as a phosphorous containing cholinesterase inhibitor type compounds.

BACKGROUND

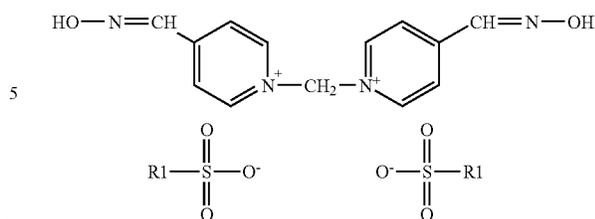
Various small bioactive molecules, once formulated, tend to be relatively unstable along with relatively short shelf life and a need for refrigeration. When dissolved in a given liquid, the activity and pharmaceutical effectiveness may be compromised. This problem has been addressed by, e.g., the preparation of freeze-dried formulations along with reconstitution as well as encapsulation and forming a liquid suspension. However, encapsulation may then interfere with in vivo performance where quick release may be desired.

The need for more stable formulations of a bioactive molecule is particular relevant with respect to the on-going need to develop treatment protocols for cholinesterase inhibiting chemicals. That is, stimulating signals are typically carried by acetylcholine within a nervous system synapse. Such signals may be discontinued by a specific type of cholinesterase enzymes, acetylcholinesterase, which breaks down acetylcholine. If cholinesterase inhibiting chemicals are present, they may then prevent the breakdown of acetylcholine thereby disrupting normal nervous system activity. For example, certain chemical classes of pesticides, such as organophosphates and carbamates, may result in toxic cholinesterase inhibition. Accordingly, if an individual is regularly exposed to such inhibitors, there remains a need to therapeutically treat such toxicity. Among other things, individuals or animals who may have been exposed to a carbamate type cholinesterase inhibitor may currently be treated with atropine, and those exposed to organophosphates may beneficially be treated with a pralidoxime antidote.

SUMMARY

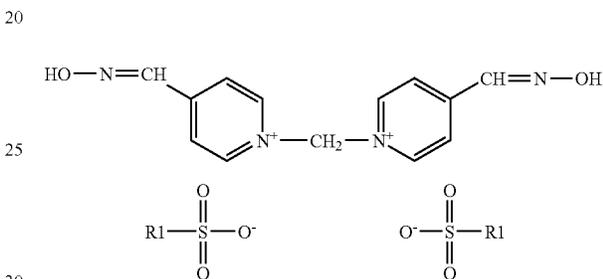
In a first exemplary embodiment, the present disclosure relates to a composition comprising a bis-quaternary pyridinium-2-aldoxime salt of the formula:

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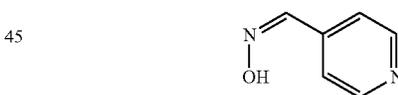
wherein R1 is a methyl and/or ethyl group wherein the salt is in particle form at a diameter of 1.0 nanometer to 100 microns and the salt is combined in a liquid wherein the solubility of the particle in the liquid is less than or equal to 10% by weight.

In a second exemplary embodiment, the present disclosure relates to a composition comprising a bis-quaternary pyridinium-2-aldoxime salt of the formula:

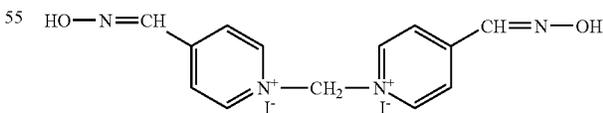


wherein R1 is a methyl and/or ethyl group wherein the salt is in particle form at a diameter of 1.0 nanometer to 100 microns and the salt is combined in a liquid wherein the solubility of the particle in the liquid is less than or equal to 10% by weight.

In a third exemplary embodiment, the present disclosure is directed at a method for preparing a liquid composition containing particles of a bis-quaternary pyridinium-2-aldoxime salt comprising supplying pyridine-4-aldoxime of the formula:



50 treating the pyridine-4-aldoxime with diodomethane to form 1,1'-methylenebis[4-[(hydroxyimino)methyl]-pyridinium]diodide of the following formula:



65 converting the 1,1'-methylenebis[4-[(hydroxyimino)methyl]-pyridinium]diodide to the following structure via ion exchange of the iodine to provide the following bis-quaternary pyridinium-2-aldoxime salt: