MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Stability-indicating HPLC method development and impurity characterization for a broad-spectrum reactivator against a highly toxic organophosphorus compound, HLö 7 dimethanesulfonate (HLö 7 DMS)

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Background Information: The threat of a deliberate release of chemical nerve agents has underscored the need to continually improve effective field treatments for these types of poisonings. Chemical nerve agents and many pesticides share an organophosphate (OP) core and have the potential to inhibit human acetylcholinesterase activity. As a treatment option, HLö 7 has been shown to be effective at low doses and without atropine, which makes it superior to HI-6. Therefore, HLö 7 has been regarded as the most powerful antidote to OP poisoning.

Purpose: Despite a number of publications describing the efficacy, synthesis, and pharmacokinetics of HLö 7 DMS, there is little information on quantitative analysis and impurity characterization in the literature, and high-performance liquid chromatography (HPLC) methods for HLö 7 have never been reported. Several HPLC methods for its similar analog, HI-6, are described in the literature. Many of the reported methods were developed for bioanalysis with liquid chromatography/mass spectrometry (LC/MS) detection and are not suitable for determining impurities and degradation products in drug substances and products. Our goal was to develop a stability-indicating HPLC method for the HLö 7 DMS drug substance in accordance with International Council for Harmonization (ICH) guideline Q2 (R1) and to identify impurities present in the drug substance and the degradation products seen in stress testing.

Methods: The study was carried out with HPLC-LC coupled with high-resolution mass spectrometry (HRMS), and nuclear magnetic resonance (NMR). The forced degradation study of HLö 7 DMS was carried out in accordance with ICH guidelines Q1A (R2) under acidic, alkaline, oxidative, thermolytic, and photolytic conditions.

Results: The separation of HLö 7 from its impurities and degradation products was achieved on an Agilent Zorbax Eclipse XDB-Phenyl column (150 mm × 3.0 mm i.d., 3.5 µm) with a gradient elution using acetonitrile and sodium 1-octanesulfonate aqueous solution as mobile-phase components. Detection was by ultraviolet (UV) light at 254 nm, and the column temperature was 35 °C. Using this method, a 0.15 µg/ml limit of detection (LOD) was determined. Liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF/MS) was used to obtain mass data for characterization of the major impurities in HLö 7 DMS drug substance. A quantitative NMR (QNMR) method was developed to determine the DMS counter ion.

Conclusions: In the future, this HPLC method could be used as a stability-indicating method suitable for the quality control and stability monitoring of the HLö 7 DMS drug substance.
Impact to the JSTO mission: The Defense Threat Reduction's Agency (DTRA) Chemical and Biological Technologies Department in its role as the Joint Science and Technology Office for Chemical and Biological Defense seek Food and Drug Administration (FDA) approval of acetylcholine reactivator drug products as a nerve agent medical countermeasure. This stability-indicating HPLC method will advance the Good Manufacturing Practice (GMP) drug substance synthesis and analytical testing activities; and thus will shorten the product development timeline for the eventual HLo-7 DMS FDA-approved product.

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