World Academy of Science, Engineering and Technology
International Journal of Chemical and Molecular Engineering
Vol:19, No:07, 2025

Methodology for Risk Assessment of Nitrosamine Drug Substance Related Impurities in Glipizide Antidiabetic Formulations

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Abstract : Purpose: The purpose of this study is to develop a methodology for the risk assessment and evaluation of nitrosamine impurities in Glipizide antidiabetic formulations. Nitroso compounds, including nitrosamines, have emerged as significant concerns in drug products, as highlighted by the ICH M7 guidelines. This study aims to identify known and potential sources of nitrosamine impurities that may contaminate Glipizide formulations and assess their presence. By determining observed or predicted levels of these impurities and comparing them with regulatory guidance, this research will contribute to ensuring the safety and quality of combination antidiabetic drug products on the market. Factors contributing to the presence of genotoxic nitrosamine contaminants in glipizide medications, such as secondary and tertiary amines and nitroso group-complex forming molecules, will be investigated. Additionally, conditions necessary for nitrosamine formation, including the presence of nitrosating agents and acidic environments, will be examined to enhance understanding and mitigation strategies. Method: The methodology for the study involves the implementation of the N-Nitroso Acid Precursor (NAP) test, as recommended by the WHO in 1978 and detailed in the 1980 International Agency for Research on Cancer monograph. Individual glass vials containing equivalent to 10mM quantities of Glipizide are prepared. These compounds are dissolved in an acidic environment and supplemented with 40 mM $NaNO_2$. The resulting solutions are maintained at a temperature of 37°C for a duration of 4 hours. For the analysis of the samples, an HPLC method is employed for fit-for-purpose separation. LC resolution is achieved using a step gradient on an Agilent Eclipse Plus C18 column (4.6 X 100 mm, 3.5µ). Mobile phases A and B consist of 0.1% v/v formic acid in water and acetonitrile, respectively, following a gradient mode program. The flow rate is set at 0.6 mL/min, and the column compartment temperature is maintained at 35°C. Detection is performed using a PDA detector within the wavelength range of 190-400 nm. To determine the exact mass of formed nitrosamine drug substance-related impurities (NDSRIs), the HPLC method is applied to LC-TQ-MS/MS with the same mobile phase composition and gradient program. The injection volume is set at 5 µL, and MS analysis is conducted in Electrospray Ionization (ESI) mode within the mass range of 100−1000 Daltons. Results: The samples of the NAP test were prepared according to the protocol. The samples were analyzed using HPLC and LC-TQ-MS/MS to identify possible NDSRIs generated in different formulations of glipizide. It was found that the NAP test generated various NDSRIs. The new finding, which has not been reported yet, discovered contamination of Glipizide. These NDSRIs are categorized based on the predicted carcinogenic potency and recommended its acceptable intact in medicines.

Keywords : NDSRI, nitrosamine impurities, antidiabetic, glipizide, LC-MS/MS
Conference Title : ICAC 2025 : International Conference on Analytical Chemistry
Conference Location : Zurich, Switzerland
Conference Dates : July 29-30, 2025