Development and Validation of Novel Analytical Methods for the Quantification and Identification of N-Nitroso Trimetazidine, a Nitrosamine Impurity, in Drug Substance and Drug Product

Sandip Vadariya
Analytical Research Development, Cohance Lifesciences Limited API R&D Centre, Ankleshwar, India

Jigar Patel
Deputy Director (Technical) Sophisticated Instrumentation Centre for Applied Research and Testing – SICART, Vallabh Vidyanagar, Anand, India

Haresh Patel
Analytical Research Development, Cohance Lifesciences Limited API R&D Centre, Ankleshwar, India

Hitin Hirpara
Research and Development Department, Cohance Lifesciences Limited API R&D Centre, Ankleshwar, India

Abstract:

In the manufacturing process of Trimetazidine hydrochloride (TMZ), N Nitroso trimetazidine (NTMZ) generate, final purification of active pharmaceutical ingredient (API) done in the presence of the charcoal, which has been identified as a possible source of nitrite. Secondary amine is present in TMZ, due to the favorable condition for nitrosamine & NDSRIs, NTMZ is generated in TMZ. Significant genotoxic and mutagenic effects of NDSRIs effect on human and regulatory requirement to control. This study is held for the trace level identification and quantification of NTMZ in TMZ drug substance and in drug product by using ultra-fast liquid chromatography-mass spectrometry/mass spectrometry (HPLC-ESI-MS/MS). The method was developed and validated for the NTMZ content in gradient mode using inert Sustain PFP (4.6 mm x 150 mm x 5 µ) column, a buffer containing 0.63 g/L ammonium formate in water and 1 mL formic acid as solution A and while solution B a mixture of methanol and acetonitrile in the ratio of 50:50 (v/v). Positive ionization in electrospray ionization (ESI) with MRM (m/z 296.15 > 181.15, 296.15 > 166.05, 296.15 > 136.15) used for NTMZ quantification and identification. The limit of detection and Quantification 0.16 ppm and 0.50 ppm respectively. The method is linear in the range of 0.5 ppm to 7.5 ppm. System precision (% RSD= 4.47), Method precision (% RSD = 1.92), intermediate precision (% RSD = 2.47), Accuracy (API: 95.16% - 126.85%, Formulation: 77.7 – 108.18 %). To identify and quantify the