Xevo TQ-S Cronos

[INDIA DEMO LAB]

A Robust and Sensitive Instrument for Quantification of N-Nitroso Nortriptyline Impurity in Amitriptyline Drug Product.

INTRODUCTION:

Recently, FDA has received additional reports of certain types of nitrosamine impurities that formed in several drug products. These nitrosamine drug substance-related impurities (NDSRIs) are a class of nitrosamines sharing structural similarity to the API.

Amitriptyline is from a group of medicines called tricyclic antidepressants. They are thought to work by increasing a chemical called serotonin in your brain. Recently there have been references that N- Nitroso nortriptyline impurity can be formed in Nortriptyline tablets due to presence of a tertiary Amino group which can interact with a nitrite group to form the NDSRI of Amitriptyline.

SCOPE OF WORK:

To overcome the analytical challenges of matrix effect and to improve the spiked recovery for N-Nitroso Nortriptyline impurity quantification in drug product needs a suitable sample preparation technique and chromatographic conditions. Waters Xevo TQ-S Cronos coupled with Acquity UPLC H-Class plus and Acquity UPLC symmetry C8 Column combination produced robust method for quantification N-Nitroso Nortriptyline impurity at method LOQ 0.03 ppm and the instrument showed excellent sensitivity with S/N ratio (>50) at 0.002 PPM level with respect to API. The observed spiked recovery was between 70 to 120% by adapting selective extraction approach. The method demonstrates linear results in the concentration range of 0.002 to 2.0ppm

Radar scan:
Understanding sample complexity, Intelligent method development & Understanding matrix effects.

RADAR is an acquisition mode that acquires both MRM and full scan MS simultaneously without compromising sensitivity, a unique capability that can both simplify and accelerate development of robust methods. During method development, RADAR offers the ability to understand unexpected results due to matrix effects The Figure 1 shows a Radar scan investigation results where API is clearly separated from the NDSRI which is eluting later. Diverting the API peak avoided the contamination of the mass spectrometer increasing the method robustness.

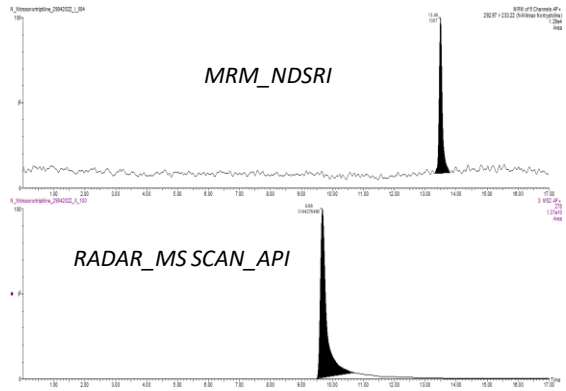

Figure 1: Chromatographic Separation of N-Nitroso Nortriptyline impurity and Amitriptyline DP by using radar scan

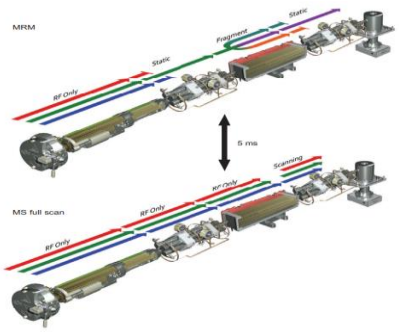

Figure 2: RADAR Functionality

Figure 3: Xevo TQ S Cronos with Acquity UPLC H-Class Plus , and Symmetry C8 Column

Test	Limit/Range
Linearity	0.002 to 2.0 ppm
Method LOQ	0.03 ppm
Instrument LOQ	0.002 ppm
Spiked recovery	98 %

Table 1: Summary for N-Nitroso Nortriptyline impurity

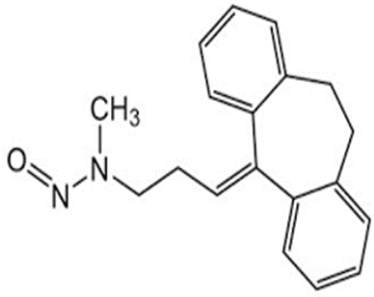

Figure 4: N-Nitroso Nortriptyline

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