Ultrasensitive LC-MS/MS Quantitation of N-Nitroso-Dabigatran Etexilate Impurity in Dabigatran Etexilate Mesylate Using Electrospray Ionization Technique

Anant D. Yadav[1,3], Ashish C. Alaspure[2,3], Sandesh R. Lodha[2], Amrutlal L. Prajapat[1], Anil H. Gore[1]*

[1]Tarsadia Institute of Chemical Science, Uka Tarsadia University, Bardoli, 394350, Gujarat, India

[2]Maliba Pharmacy College, Uka Tarsadia University, Maliba Campus, Gopal Vidyanagar, Bardoli, 394350, Gujarat, India

[3] Analytical Research and Development, Alkem Laboratories Ltd., Bharuch, 393010, Gujarat, India

Corresponding Author: Dr. Anil H. Gore Email: anilanachem@gmail.com

Table S1: Optimized tandem mass spectrophotometer (MS/MS) parameters and time segments.

Parameters	Values		
Ionization mode	+ve		
Gas temperature	350˚C		
Nebulizer	25 psi		
Sheath gas temperature	350˚C		
Sheath gas flow	12 L/min		
Capillary	3500 V		
Nozzle Voltage	500 V		
Scan segments			
Compound Name	N-nitroso-dabigatran etexilate (NDE)		
Precursor Ion	657.2		
Product Ion	364.1		
Dwell	200		
Fragmentor (V)	20		
Collision Energy (V)	20		
Cell accelerator voltage (V)	3		
Polarity	+ve		
Time segments			
Start time (min)	**Scan Type**	**Valve**	**Delta EMV**
0	MRM	To Waste	500
16.7	MRM	To MS	500
25	MRM	To Waste	500

Table S2: Summary of linearity results for solutions from LOD to 200% of the limit level.

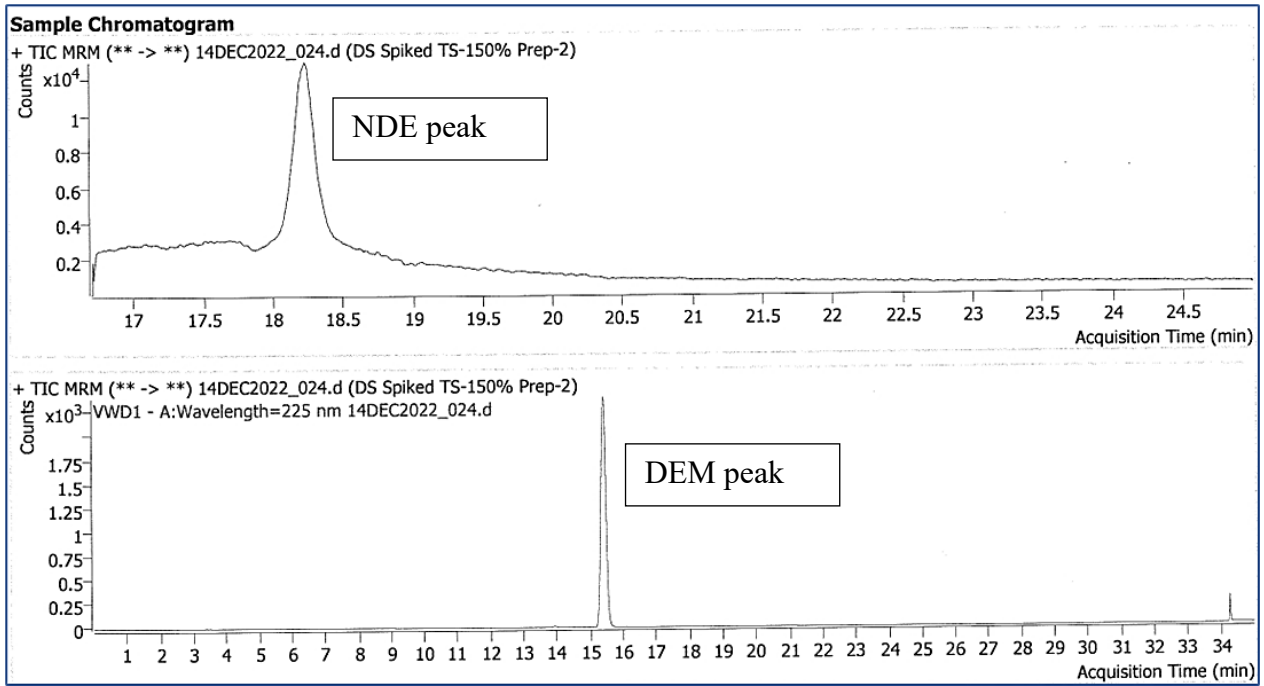| Linearity level w.r.t 60 ppb	NDE	
	Concentration (ng/mL)	**Area response**
10% (LOD)	0.0604	7191
30% (LOQ)	0.1812	18535
50%	0.3021	31965
80%	0.4833	50999
100%	0.6041	57388
150%	0.9062	85185
200%	1.2083	114359
Correlation coefficient		0.999
Slope		92202.9
Intercept		2895.2

Fig. S1: TIC and UV chromatogram showing the separation of NDE impurity from DEM drug peak.
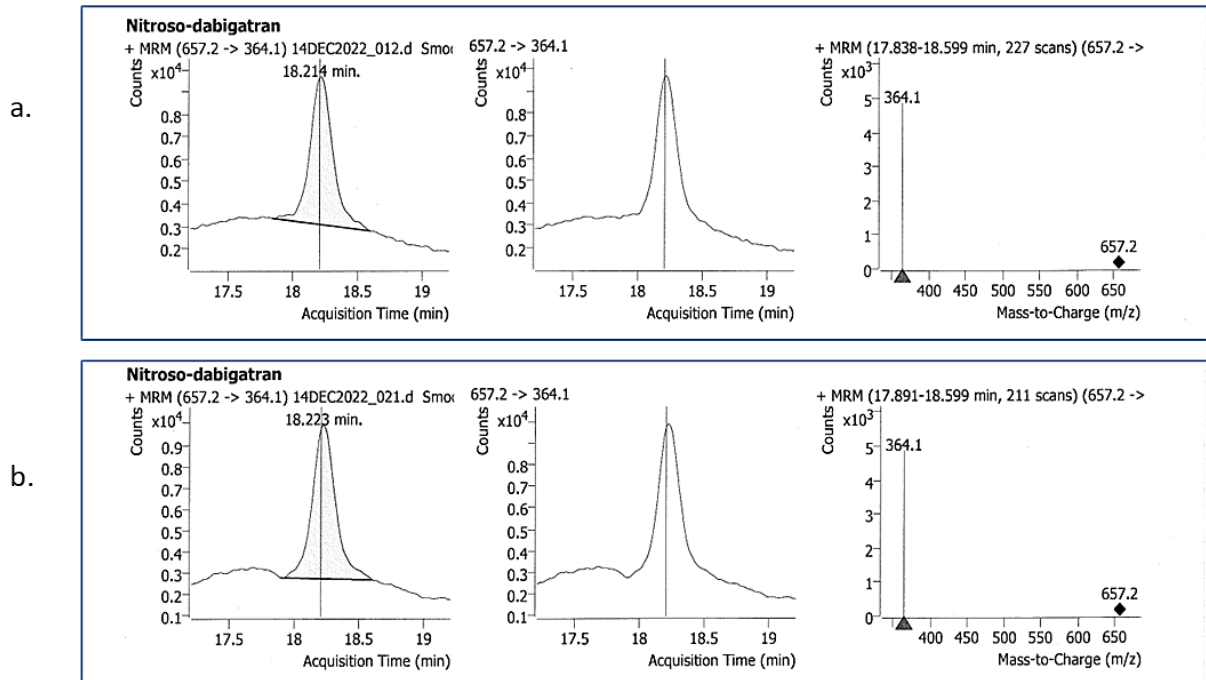

Fig. S2: a. NDE spiked with drug product and b. NDE spiked with drug substance.