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Ion funnel quadrupole time of Flight mass spectrometry: optimization for achieving all ion MS/MS and pseudo MS^n

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Abstract: An attempt has been made to study and understand Ion funnel technology for improved detection and measurement capabilities of ions originating from small molecules. Different ways to create and study collision induced fragments have been explored and strategies to achieve various kinds of all ions MS/MS have been discussed. We observed that stability of ions in the system is largely controlled by the funnel exit DC voltage and Rf voltages of the low pressure funnel also contributes to the collision induced dissociation of the ions. An appropriate mix of in source collision energy coupled with Funnel exit DC voltage and low pressure funnel Rf voltage can induce extensive fragmentation of the ions mimicking several stages of MS/MS simultaneously.

Keywords: Ion funnel; QTOF, optimization, All ion MS/MS, Pseudo MS^n.

INTRODUCTION

The ever expanding role of mass spectrometry in research has been instrumental in prompting researchers to find newer and better techniques (Fenn *et al.,* 1990, Takats *et al*., 2004, Creaser and Redcliffe, 2006) for creating ions and their smooth and seamless transmission inside the mass spectrometers, since creation, transfer and transmission of ions have been the major factors limiting the capabilities of the present day mass spectrometers. Most of the commercial mass spectrometers conventionally employ an aperture with a tiny hole, often a narrow bore capillary followed by a conductance-limiting orifice, usually called skimmer which helps to remove, albeit partially the inert gas, usually nitrogen and neutrals which might have reached there because of the voltages and vacuum differentials. However this set up does produce a reasonably laminar flow of ions into the mass spectrometer. Unfortunately this combination of capillary and skimmer allows only a small fraction of the ion cloud to enter the ion optics and thus is a major sensitivity bottleneck. In order to improve the quality and quantity of the ions entering the mass spectrometer, Shaffer *et al.* (1997, 1998, 1999) developed ion funnel technology as a replacement for the ion transmission-limited skimmer, seeking to ensure the near lossless transmission of ions. A much larger aperture, usually in the form of a capillary having multiple bores is used to introduce much larger quantity of ions. The defining features of the ion funnel are a series of closely spaced ring electrodes whose inner diameters gradually decrease serving to radially confine ions as they pass through creating a near ideal laminar flow of ion beam devoid of neutrals and erratic movements of ions. Out-of-phase Rf potentials are applied to adjacent electrodes, and a dc gradient is typically applied along the axis of the ion funnel to drive ions through the device. The use of dual offset ion funnels further improves the efficiency by increasing ion transmission, and removing neutrals. Electrodynamic ion funnels of 'hourglass' design have been developed to efficiently accumulate and pulse ions into the system there by achieving essentially lossless transmission of ions on to QTOF across the range of ion masses relevant to most applications (Tang *et al*., 2005). The theory, implementations and applications of ion funnel technology has recently been reviewed (Kelly *et al*., 2010). Use of ion funnel at ambient pressure to enhance the sensitivity of extractive electrospray ionization (EESI) by spraying directly into the ion funnel has been recently reported (Meier *et al*., 2012). Advent of high resolution instruments and their commercial availability has enabled analysis of complex mixtures of ions produced by high energy collision induced dissociations without a dedicated collision cell. Targeted data extraction of the MS/MS spectra generated by data independent acquisition is a new concept in consistent and accurate proteome analysis in high resolution environment. (McAlister *et al*., 2011, Gillet *et al* ., 2012). The ion funnels have enabled the manipulation and focusing of ions in a pressure regime (0.1–30 Tor) that has defied attempts made under traditional approaches. In a conventional capillary-skimmer type of system, the voltages differential between the capillary exit and the

skimmer may lead to fragmentation of the ions present in the system, the extent of the fragmentation behavior being largely controlled by potential difference and nature of the ions present in the ion cloud. Understandably controlling this potential difference is the only major possible way of creating fragment ions in MS only instruments {Time of Flight (TOF) and single quadruple; (SQ)}. However an ion funnel provides an unprecedented control on transmission and fragmentation of ions, which when appropriately exploited allows the user to achieve higher sensitivity, targeted data acquisition, rapid quantitative method development in an all ions MS/MS mode as well as pseudo multiple MS^n in a QTOF/QQQ environment.

In the present study, we have made an attempt to understand the various funnel parameters, in source collision energy in MS mode so as to achieve proper transmission and fragmentation of ions and which can then be used for various purposes including pseudo MS^n, a prerequisite for de novo structure elucidation. Role of funnel exit DC voltage vis-à-vis conventional fragmentor voltage has been explored.

MATERIALS AND METHODS

Materials: Caffeine (5190-0488), reserpine ((G1946-85004) and mixture of four sulfa drugs (sulfamethizole, sulfamethazine,sulfachloropyridazine and sulfadimethoxine in water, P/N 59987-20033) were supplied byAgilent Technologies. All solvents, acetic acid, and formic acid were of HPLC grade or better (Fisher Scientific).

Instrumentation: The chromatographic system consisted of an Agilent 1290infinity series HPLC system, comprising of a binary pump (G4220A), an isocratic pump (G1310B), column oven (G1316C), High pressure autosampler (G4226A)) with thermostat (G13308) and flex cube (G4227A), a diode array detector (G4212A), coupled with an ion funnel QTOF mass detector (G6550A) equipped with dual spray ESI and Agilent jet stream ESI source. Agilent's Masshunter software was used to acquire (Acquisition software version B05.01 Build5.01.5126) and analyze (Qualitative Data analysis software version B.06.00 Build 6.0633.0) LCMS data.

Chromatographic conditions: Chromatography of basic compounds and sulfa drugs compounds was performed on a Zorbax-SB C_{18}guard column (2.1x12.5 mm, 5 µm), maintained at 40°C. The flow rate was set at 0.3 mL/min and the eluent was 72% acetonitrile in water containing 0.1% acetic or formic acid. For steroidal compounds a fast gradient of 40 to 80% acetonitrile (90%) in 60 s at a flow rate of 0.5 ml was used. The compounds were analyzed using electro-spray ionization (dual ESI) in positive mode. Operating conditions were: drying gas (N_2) 14 L/min; drying gas temperature 290°C; nebullizer pressure 35 psi; capillary voltage 3500 V (4500 V for steroidal compounds); and fragmentor voltage 350 V. Mass spectra were acquired in 50-1100 mass range at a rate of 4 spectra /s in MS as well as MS/MS mode using m/z 121.050873 and m/z 922.009798 as internal reference masses. Funnel parameters: Funnel exit DC voltage was varied from 20V to 120 V, and voltage drop and Rf voltage of high and low pressure funnels were studied in a range of 25V to 200V.

The standard stock solutions (1 mg/mL) of compounds, where necessary, were prepared by dissolving separately 10 to 25 mgcompound in methanol. Working solutions were prepared by serial dilution in the concentration range of 10 to 100 pg in 1µl of methanol-water (1:1)

RESULTS AND DISCUSSIONS

Ion-funnel ESI-MS interface consists of a multi-capillary (6X600 µm) inlet and dual ion funnels, called high pressure and lowµpressure funnel respectively. An offset between the multi-capillary inlet and the first high pressure ion funnel is used to reduce chemical background. A static potential bias is applied to the ion guide to move the ions forward through the ion guide from the ion inlet, at high pressure, to the analyzer, located at low pressure, therefore DC voltage is dropped across high pressure as well as low pressure ion funnel. The unruly ion beam which enters the two funnel system through multi-capillary inlet is compressed and smoothened by applying time varying potentials (similar RF amplitudes, but 180°C out-of-phase) which also improves the transmission efficiency of ions across a differential vacuum orifice located at the exit of these funnels. Finally a DC voltage (FDC) is applied to the last electrode of the low pressure ion funnel so as to propel the ion beam through and beyond octopole.

Fragmentor voltage: The voltage differential between the exit end of the capillary and skimmer is responsible for transmission as well as collision induced non-specific fragmentation of ions and hence voltage applied at capillary exit is often termed fragmentor voltage. However there are no skimmers in ion funnel systems. The fragmentor in the ion-funnel systems is kept at 350 V. This value may seem excessively high, but the delta voltage between the fragmentor and the high pressure ion funnel entrance is minimal since the high pressure ion funnel entrance voltage is also set at ~350 V. In contrast, non-ion funnel systems have much higher (100±20V or even more) delta voltage between skimmer and capillary exit which controls ion transmission as well as fragmentation. This difference becomes all the more prominent when one considers delta voltage per unit distance since the distance between capillary exit and octopole is far greater in ion-funnel systems than in conventional systems. Therefore, the differing delta voltage (between the capillary exit and the next optical

element) is different for i-Funnel systems vs. non-i-Funnel systems. Consequently fragmentor voltage has minimal influence on fragmentation of ions entering the ion funnel system. We also observed fragmentor voltage to not exert any significant influence upon fragmentation of ions and lowering its value below 300V reduced ion abundances as well. However, as discussed later, we observed that role played by fragmentor in fragmenting the ions has largely been overtaken by funnel DC voltage.

Funnel Rf voltage: We studied transmission of caffeine (I) at m/z 195.0877 $[M+H]^+$; reserpine (II) at m/z 609.2807 $[M+H]^+$; Sulfamethizole (III) at m/z 271.0317 $[M+H]^+$; Sulfamethazine (IV) at m/z 279.0910 $[M+H]^+$; Sulfadimethoxine (V) at m/z 311.0809 $[M+H]^+$; sulfachloropyridazine (VI) at m/z 285.0208 $[M+H]^+$; Dehydroepiandrosterone , DHEA (VII) at m/z 271.2056 $[M+H-H_2O]^+$; 7-oxo-DHEA (VIII) at m/z 285.1849 $[M+H-H_2O]^+$; and progestrone (IX) at m/z 315. 2319 $[M+H]^+$ (Fig. 1). Extracted ion spectra were obtained from total ion current chromatograms (TIC) using a 20 ppm window. DHEA (VII) and 7-oxo-DHEA (VIII) were found to undergo extensive neutral loss of water and hence were studied $[M+H-H_2O]^+$ for ion. These compounds were studied with respect to ion funnel parameters viz. DC voltage drop, Rf voltage and Funnel DC voltage. The effect of varying Rf voltage applied across high pressure funnel is shown in Fig 2. The best ion abundances were obtained between 100-150 Volt range for high pressure funnel; however, the transmission of reserpine ion (m/z 609) continuously improved across the voltage range studied (50-200 V) which can probably be attributed to higher molecular weight and the absence of labile groups on the molecule. Among sulfa drugs best sensitivity was exhibited by those having electron donating groups (+I effect) in the aromatic system (IV & V) whereas least sensitivity was observed for sulfachloropyridazine (VI) understandably because of the presence of chlorine (-I effect) in the aromatic system. Among the three steroids studied progesterone (IX) and 7-oxo-DHEA showed similar behavior as compared to DHEA (VII); lower response of DHEA (VII) can be attributed to its lower polarity when compared to VIII and IX. However 7-oxo-DHEA (VIII) and DHEA (VII) underwent preferential neutral loss of water, and we found it difficult to prevent this neutral loss under present conditions. From these observation, it may be concluded that minimal fragmentation (except preferred neutral losses when dictated by the organic chemistry of the molecule) occurs in the high pressure funnel region of the ion funnels; this was contrary to our expectations, since we were expecting more collision induced fragmentations in the high pressure funnel due to presence of nitrogen gas at higher pressure. The only logical explanation we can offer for this behavior is absence of the sufficient kinetic energy in transmitting ions since virtually there is no significant voltage differential between capillary exit voltage (~350 V) and high pressure ion funnel entrance voltage (~350 V).

However scenario is a little different in low pressure funnel area; the voltage differential applied along high pressure ion funnel does impart some kinetic energy into the ions which now enter the second funnel with more kinetic energy; consequently increasing the Rf voltage across low pressure ion funnel results in higher energy collision induced dissociations resulting in fragmentations of the major ion species present in the system (Fig. 3). The loss of abundance of major ions resulted in a tandem increase in the abundance of their major fragments (not shown). We observed that an Rf voltage of 50 to 100V was sufficient to transmit small ions (m/z 200-400) across the low pressure funnel, increasing this voltage beyond 100 V often increased the CID induced fragmentations; the onset of fragmentation was gradual and dependent upon the chemistry of the molecule, but never the less almost all the molecules suffered fragmentation at or above 150 V and sometimes with drastic impact at 175-200V. Again the reserpine was the exception and refused to undergo any appreciable fragmentation probably due to higher

Table 1. Mass spectrum of caffeine at 80 V funnel exit DC, 20 V source collision cell energy.

	MS data			Auto MS/MS of m/z 195	
Ion Formula	**$[M+H]^+$ Theoretical**	**$[M+H]^+$ Observed Error (ppm)**	**% Abundance**	**$[M+H]^+$ Observed Error (ppm)**	**% Abundance**
$C_8H_{11}N_4O_2$	195.08765	3	46.5	0.6	35.3
$C_6H_8N_3O$	138.06619	3.9	100	0.1	100
$C_5H_5N_3O$	123.04271	3.7	11.4	4.7	3.9
$C_5H_8N_3$	110.07127	3.6	20.4	1.9	1.9
$C_4H_4N_2O$	96.03181	ND	ND	ND	ND
$C_4H_5N_3$	95.0478	6.4	0.2	ND	ND
$C_4H_7N_2$	83.06037	4.6	15.7	1.3	1.6
$C_3H_4N_2$	68.0369	4.9	2.9	ND	ND
C_3H_6N	56.04948	1.1	6.7	9.5	12
C_2HN_2	53.01342	0.2	0.7	ND	ND

ND: Not detected

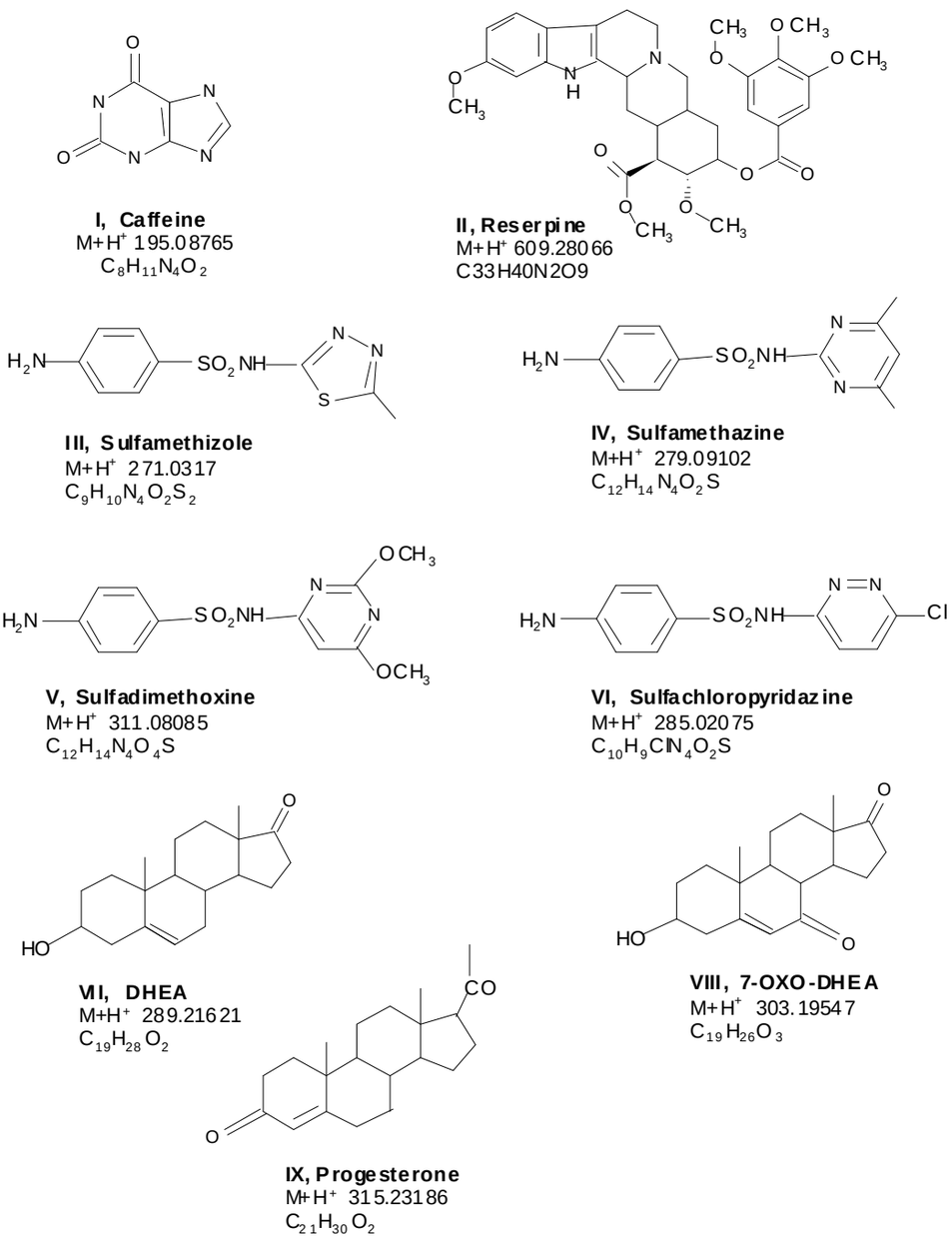

Fig. 1. *Chemical structures of the compounds used in the study.*

molecular weight.

Funnel voltage drop: The extent of DC voltage drop across both funnels (Fig 4 and 5) had no appreciable and even detectable influence on the fragmentation of the major ions. However both funnels do differ in their behavior in this respect too. Increasing the delta voltage (50 to 200 V) across high pressure funnel continually improved the transmission of the ions and no maxima was observed for any of the compound studied (Fig. 4), In contrast, in low pressure funnel ion transmission improved up to a delta voltage of 50 V; and increasing the delta voltage beyond 50 V resulted in the creation of plateau of Tibet, with no appreciable change in the intensity of the signals (Fig. 5).

Funnel DC: The funnel DC is the voltage applied to the last electrode of the low pressure funnel and helps in transmitting the ions into octopole and beyond. In this sense it is akin to the fragmentor voltage applied to the capillary exit in the non-ion funnel mass spectrometers. We found the Funnel DC voltage also behaves similar to the conventional fragmentor voltage. Lower Funnel DC voltages (30 to 50 V) helped in the transmission of the major ion of the molecules in question but increasing this value beyond 60 volt resulted in collision induced fragmentations and values beyond 80V resulted in

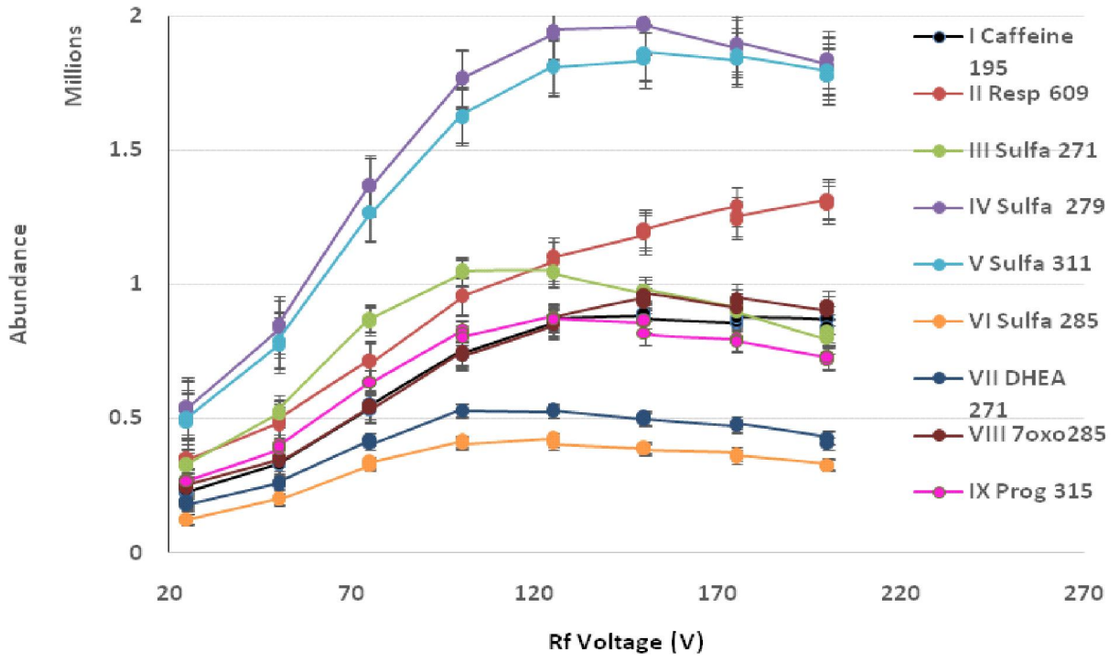

Fig. 2. *Effect of high pressure funnel Rf voltage on the ion transmission. I: caffeine at m/z 195.0877 $[M+H]^+$; II: reserpine at m/z 609.2807 $[M+H]^+$; III: Sulfamethizole at m/z 271.0317 $[M+H]^+$; IV: Sulfamethazine at m/z 279.0910 $[M+H]^+$; V: Sulfadimethoxine at m/z 311.0809 $[M+H]^+$; VI: sulfachloropyridazine at m/z 285.0208 $[M+H]^+$; VII: Dehydroepiandrosterone, DHEA at m/z 271.2056 $[M+H-H_2O]^+$; VIII: 7-oxo-DHEA at m/z 285.1849 $[M+H-H_2O]^+$; and IX: progestrone at m/z 315. 2319 $[M+H]^+$. Extracted ion spectra were obtained from total ion current chromatograms (TIC) using a 20 ppm window.*

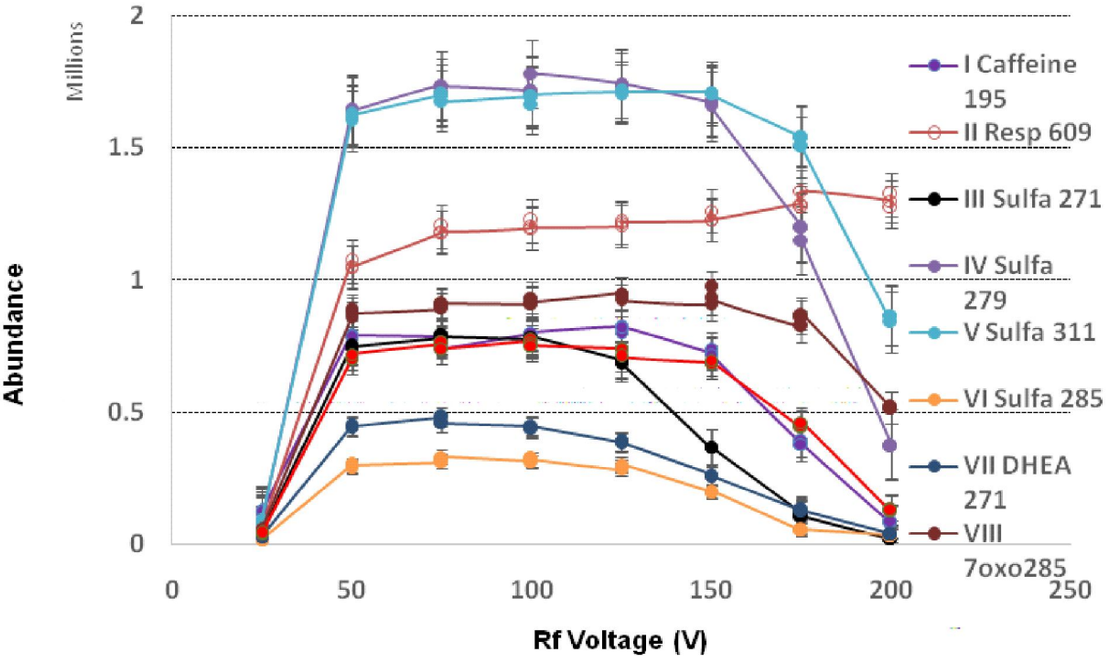

Fig.3. *Effect of low pressure funnel Rf voltage on the ion transmission. I: caffeine at m/z 195.0877 $[M+H]^+$; II: reserpine at m/z 609.2807 $[M+H]^+$; III: Sulfamethizole at m/z 271.0317 $[M+H]^+$; IV: Sulfamethazine at m/z 279.0910 $[M+H]^+$; V: Sulfadimethoxine at m/z 311.0809 $[M+H]^+$; VI: sulfachloropyridazine at m/z 285.0208 $[M+H]^+$; VII: Dehydroepiandrosterone ,DHEA at m/z 271.2056 $[M+H-H_2O]^+$; VIII: 7-oxo-DHEA at m/z 285.1849 $[M+H-H_2O]^+$; and IX: progestrone at m/z 315. 2319 $[M+H]^+$. Extracted ion spectra were extracted from total ion current chromatograms (TIC) using a 20 ppm window.*

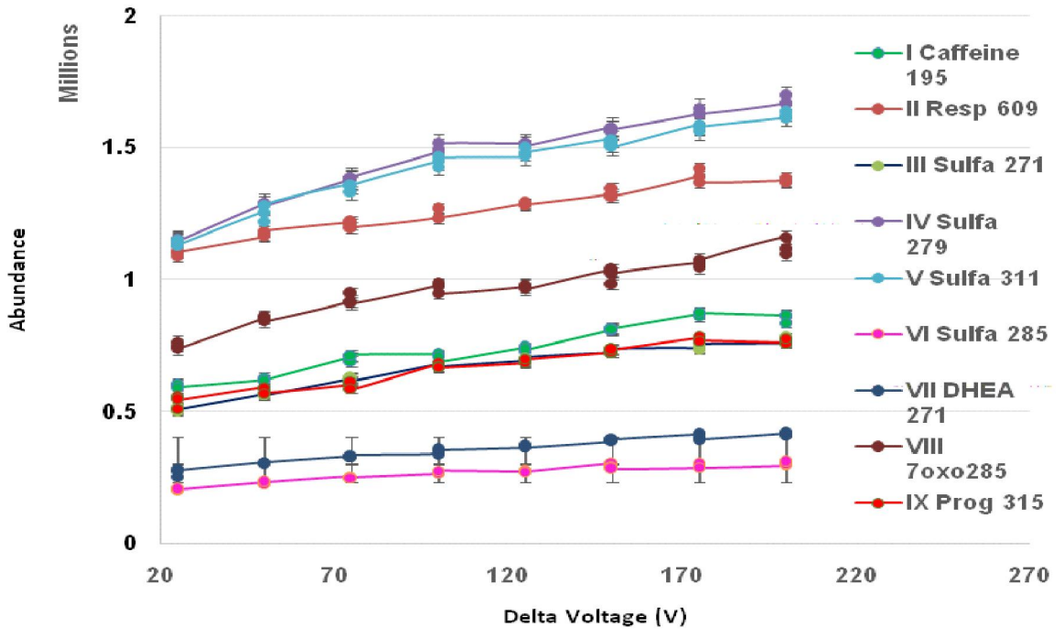

Fig.4. *Effect of DC voltage drop across high pressure funnel on the ion transmission and dissociation. I: caffeine at m/z 195.0877 [M+H]⁺; II: reserpine at m/z 609.2807 [M+H]⁺; III: Sulfamethizole at m/z 271.0317 [M+H]⁺; IV: Sulfamethazine at m/z 279.0910 [M+H]⁺; V: Sulfadimethoxine at m/z 311.0809 [M+H]⁺; VI: sulfachloropyridazine at m/z 285.0208 [M+H]⁺; VII: Dehydroepiandrosterone ,DHEA at m/z 271.2056 [M+H-H₂O]⁺; VIII: 7-oxo-DHEA at m/z 285.1849 [M+H-H₂O]⁺; and IX: progestrone at m/z 315. 2319 [M+H]⁺. Extracted ion spectra were extracted from total ion current chromatograms (TIC) using a 20 ppm window.*

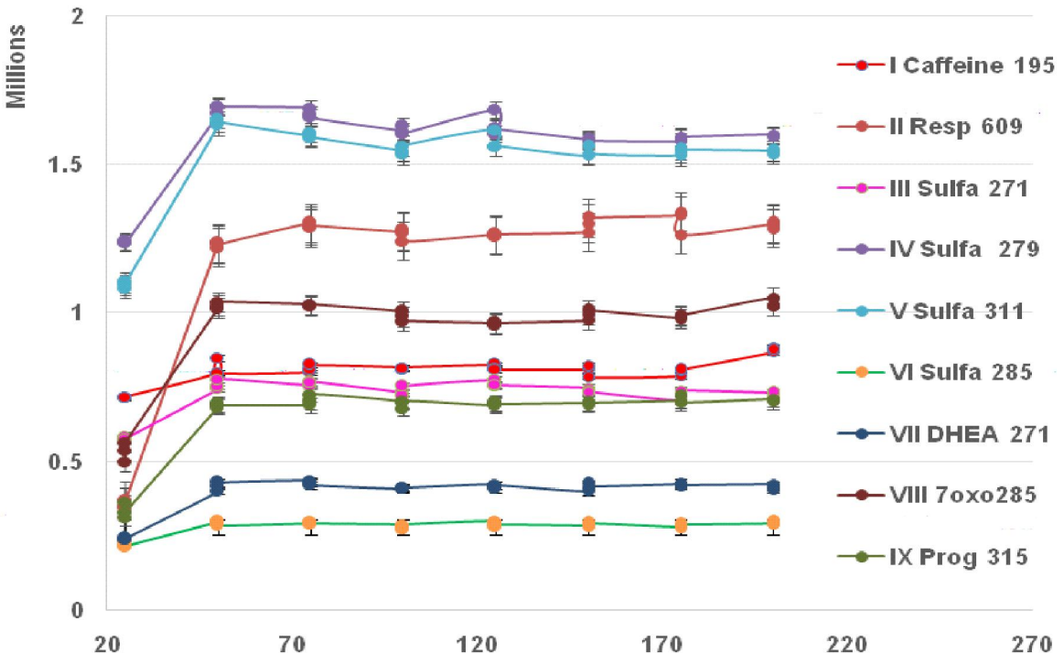

Fig.5. *Effect of DC voltage drop across low pressure funnel on the ion transmission and dissociation. I: caffeine at m/z 195.0877 [M+H]⁺; II: reserpine at m/z 609.2807 [M+H]⁺; III: Sulfamethizole at m/z 271.0317 [M+H]⁺; IV: Sulfamethazine at m/z 279.0910 [M+H]⁺; V: Sulfadimethoxine at m/z 311.0809 [M+H]⁺; VI: sulfachloropyridazine at m/z 285.0208 [M+H]⁺; VII:* Dehydroepiandrosterone, DHEA at m/z 271.2056 [M+H-H₂O]⁺; *VIII: 7-oxo-DHEA at m/z 285.1849 [M+H-H₂O]⁺; and IX: progestrone at m/z 315. 2319 [M+H]⁺. Extracted ion spectra were extracted from total ion current chromatograms (TIC) using a 20 ppm window.*

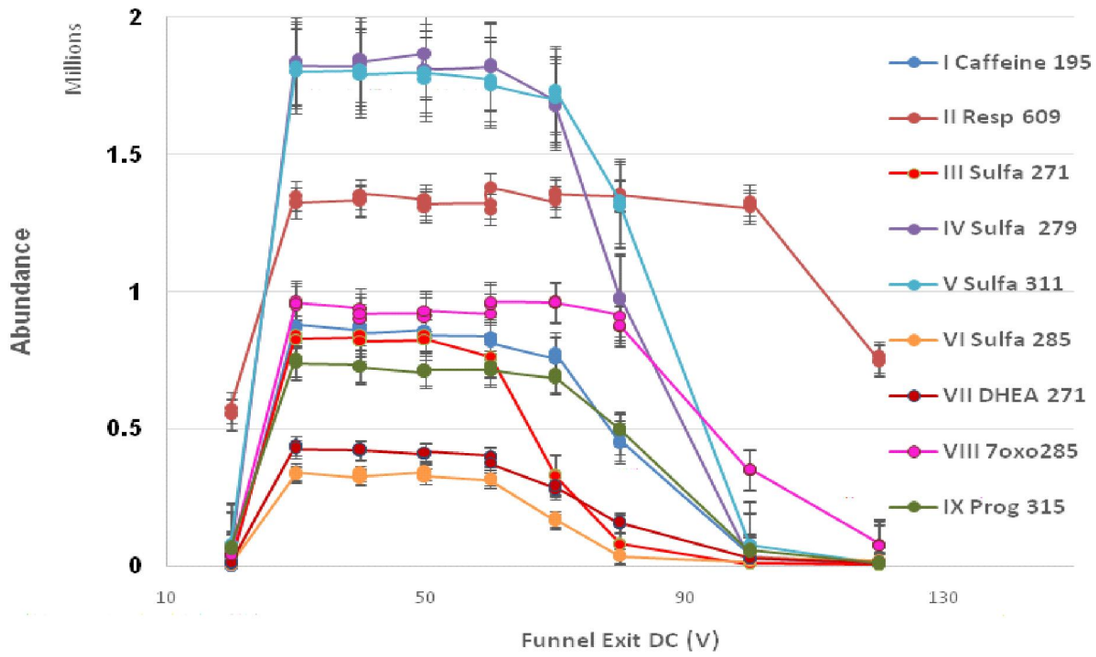

Fig.6. *Effect of funnel exit DC voltage applied to the last electrode of low pressure ion funnel on the ion transmission and dissociation. I: caffeine at m/z 195.0877 $[M+H]^+$; II: reserpine at m/z 609.2807 $[M+H]^+$; III: Sulfamethizole at m/z 271.0317 $[M+H]^+$; IV: Sulfamethazine at m/z 279.0910 $[M+H]^+$; V: Sulfadimethoxine at m/z 311.0809 $[M+H]^+$; VI: sulfachloropyridazine at m/z 285.0208 $[M+H]^+$; VII: Dehydroepiandrosterone ,DHEA at m/z 271.2056 $[M+H-H_2O]^+$; VIII: 7-oxo-DHEA at m/z 285.1849 $[M+H-H_2O]^+$; and IX: progestrone at m/z 315. 2319 $[M+H]^+$. Extracted ion spectra were extracted from total ion current chromatograms (TIC) using a 20 ppm window.*

appreciable dissociation of ions. Even the reserpine was appreciably degraded at 120 V. However the maximum tolerable funnel DC value for a compound depends upon its molecular weight and chemical stability of the ion of the interest under elctromagnetic fields; as a general rule heavier and stable molecules can withstand higher Funnel DC voltages. In a QQQ and QTOF instruments one does have the option of applying collision energy without isolating any ion; therefore an intelligent combination of collision energy and funnel DC voltage along with Rf voltage of low pressure ion funnel can be used to induce almost any kind of fragmentation pattern for pseudo MS^n studies. This is discussed below taking caffeine as an example. However, it may be worth mentioning that higher Funnel DC voltage and at higher source collision energy also cause fragmentation of reference ions, particularly towards the lower end of the mass spectrum. So appropriate additional concentrations of the reference ions should be used for accurate mass measurements. We observed that at about 100 V funnel DC lower reference mass of m/z 121 suffered about 90% collision induced dissociation when compared to its abundance at 30-50 V funnel DC.

Caffeine (I) is one of the most commonly used standards for small molecule in mass spectrometry and its mass behavior has been studied well (NIST, Peterson et al. 2004). It under goes extensive fragmentation in MS/MS mode to give a series of ions. We studied the mass spectral behavior of caffeine under different conditions of funnel exit DC voltage, source collision energy in MS mode and Rf voltage of low pressure ion funnel. Each parameter induced fragmentation of caffeine to some extent; eventually by using a combination of funnel exit DC voltage and in source collision energy we were able to induce and obtain in MS mode most of the major fragments reported for caffeine (Table 1) in good ppm accuracy. It was not possible to obtain all these fragments simultaneously by auto and/or targeted MS/MS of caffeine (Table 1). This has a serious implication for achieving pseudo MS^n (n=3-5) of compounds in QTOF and is subject matter of our current research efforts. As an added bonus daughter ions can be seen in MS mode along with reference ions, which is extremely helpful in *de novo* structure elucidation studies. A judicious use of these parameters can be used to achieve reasonable abundance of daughter ions in MS mode, which is a prerequisite for achieving good results in all ion MS/MS studies and for achieving different patterns of high energy collision induced dissociations (CID) without using a dedicated collision cell (Coon *et al.*, 2011).

Conclusion

Ion funnel allows unprecendented control of ion transmission and fragmentation than conventional

capillary orifice-skimmer system of mass spectrometers. But much higher flow and better control on the ion beam comes with a price, since sometimes it may be difficult to transmit unstable ions across the ion funnel intact. However greater control allows the mass spectrometerist to create different patterns of all ion MS/MS spectra as well as collision induced dissociations without using a dedicated collision cell for further advanced studies; and at the same time fragment ions can be seen in MS mode along with reference ions, which is extremely helpful in *de novo* structure elucidation studies.

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