



(51) International Patent Classification:

H01J 49/04 (2006.01) *B05B 5/025* (2006.01)
H01J 49/26 (2006.01)

(21) International Application Number:

PCT/US2014/014221

(22) International Filing Date:

31 January 2014 (31.01.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/759,645 1 February 2013 (01.02.2013) US
13/827,727 14 March 2013 (14.03.2013) US

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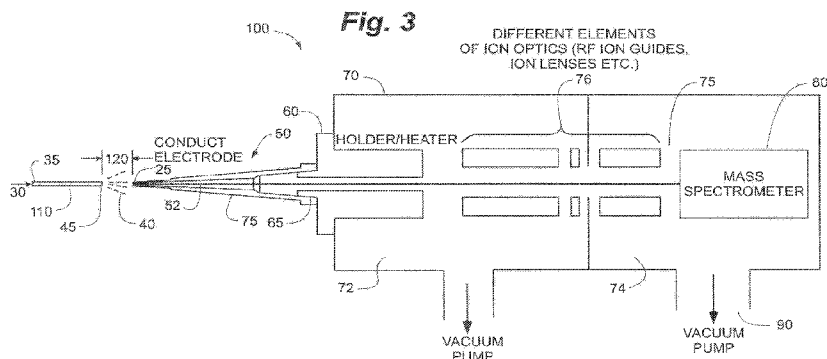
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: IMPROVING ION TRANSMISSION INTO A MASS SPECTROMETER



(57) Abstract: An ion transfer device for transferring ions emerging from an electrospray ion source at atmosphere to a vacuum chamber includes an inner surface in the shape of a diverging conical duct. The ion transfer device has an entrance aperture for positioning proximate the exit port of the electrospray ion source emitter, the entrance aperture receiving the electrosprayed ions from the exit port of the electrospray ion source emitter at atmosphere, the diverging conical duct being an electrode toward which the ions migrate and having an exit aperture with an inner diameter larger than an inner diameter of its entrance aperture, the exit aperture enclosed in the vacuum chamber, the diverging conical duct transporting the ions from atmosphere to vacuum. The vacuum chamber can be a chamber of a vacuum housing enclosing a mass analyzer.

IMPROVING ION TRANSMISSION INTO A MASS SPECTROMETER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is an International PCT application and claims priority to pending U.S. Serial No. 13/827,727, filed March 14, 2013, which in turn claims priority to pending U.S. Provisional Application No. 61/759,645, filed February 1, 2013, the entireties of which are incorporated herein by reference thereto.

STATEMENT REGARDING FEDERALLY FUNDED RESEARCH

[0002] This invention was made with government support under grants RR00862 and GM103314 awarded by the National Institutes of Health. Accordingly, the government has certain rights in the invention.

TECHNICAL FIELD

[0003] The present disclosure relates to a method and apparatus for improving ion transmission into a mass spectrometer, and, more particularly, to a method and apparatus for improving the transfer of ions between atmosphere and a vacuum region of a mass spectrometer, and to a mass spectrometer with improved ion transfer thereto.

BACKGROUND

[0004] The performance of scientific instruments, such as mass spectrometers, which operate under vacuum conditions with the ions of interest produced externally at atmospheric pressure are profoundly affected by the efficiency of ion transfer between the atmosphere and vacuum regions of the instrument. As transfer efficiency increases, loss of ions produced from the sample of interest is reduced, and the number of informative ions that enter the instrument is increased. This can result in increased speed of analysis, resolution, and sensitivity of the instrument.

[0005] Among the most rudimentary atmosphere–vacuum interfaces is a small orifice in the first vacuum chamber evacuated by a roughing pump to pressures of about 1–10 Torr. The pumping speed of typical roughing pumps is usually a few liters/s, which places a limit on the diameter of the orifice of typically less than 0.5 mm. Ion beams created this way are usually poorly collimated, so that the beam diameter quickly increases downstream of the orifice. To avoid destroying the ion beam and incurring ion losses, a skimmer electrode is typically positioned 4–7 mm downstream of the orifice to provide a means for ion passage further into the next higher vacuum stage of the instrument, as described, for example, in a publication by Fenn, “Mass spectrometric implications of high-pressure ion sources,” *Int. J. Mass Spectrom.* **2000**, 200: 459–478.

[0006] The first atmosphere–vacuum interfaces for coupling electrospray ionization (ESI) sources to mass spectrometers were designed on this principle, and some mass spectrometer manufacturers still use this design with little or no modifications. One disadvantage of this rudimentary interface is the absence of an efficient means to supply heat to the small charged droplets produced by ESI and the associated heavily solvated ions after they have entrained in the supersonic jet formed by gas expansion into the vacuum.

[0007] The effects of adiabatic expansion cooling can be counteracted to some extent by creating a declustering potential between the orifice and the skimmer. However, the amplitude of the declustering voltage cannot be very large because it will induce dissociation of the already desolvated ions. Other modifications to this rudimentary interface previously proposed to improve the ion desolvation process include introducing a counter flow of heated gas (sometimes referred to as a heated gas curtain), heating the entire interface, and installing a heated laminar flow chamber (particle discriminator interface, PDI) in front of the orifice. However, these modifications are expensive, and/or frequently of very limited efficiency, often requiring precise controls for optimization of temperature and gas flows for the particular analyte and solvent system. Such controls are needed to insure complete desolvation and to prevent a decrease in sensitivity from ions being swept away at gas flow rates that are too high.

[0008] One efficient solution to improving the ion desolvation process without the need for precise gas flow control is described in co-owned U.S. Patent No. 4,977,320 to Chowdury, *et al.*, (hereinafter, “Chowdury”), entitled “Electrospray Ionization Mass Spectrometer with New Features,” which issued on December 11, 1990. In the method disclosed by Chowdury, solvated ions formed by an electrospray ionization of an analyte solution at atmospheric pressure were introduced into a first vacuum chamber of a mass spectrometer through a metal capillary heated to, for example, about 85° C. The capillary in Chowdury is about 0.5 mm in diameter and of 203 mm in length, and projects into the first vacuum chamber 21 of the mass spectrometer. Chowdury further discloses that heating of the capillary tube causes evaporation of the droplets and desolvation of the resulting molecular ions of interest for analysis. Such ion interfaces containing a heated metal capillary or an array of heated capillaries instead of a simple orifice have since become widely adopted by mass spectrometry manufacturers and researchers, especially when high flow-rate ESI ion sources are coupled to mass spectrometers.

[0009] With the advent of nano-flow ESI ion sources, or low flow-rate electrospray ionization sources, the sensitivity of mass spectrometers coupled to on-line chromatography has dramatically increased (*see, e.g.*, U.S. Patent No. 5,788,166 to Valaskovic, *et al.*, entitled “Electrospray ionization source and method of using the same,” issued August 4, 1998). Nano-flow ESI emitters can potentially provide better conditions for sample ionization and, ultimately, higher ionization efficiency than the standard electrospray sources based on the heated metal capillary as described in Chowdury. However, little optimization has been made to ion interfaces that operate with nano-flow ESI sources to increase the efficiency of ion transfer between the atmosphere and the vacuum interface of a mass spectrometer.

[0010] Accordingly, there is still a need for a method and apparatus for improving the transfer of ions from atmosphere into a vacuum region of a mass spectrometer, particularly for mass spectrometers for coupling nano-flow ESI ion sources thereto.

SUMMARY

[0011] The present disclosure provides a method and device for improving the transfer of ions from atmosphere into a vacuum stage of a mass spectrometer. The present disclosure additionally provides a mass spectrometer including the ion transfer device for coupling an ESI ion source thereto.

[0012] In one aspect, a system for the analysis of the mass spectra of ions includes an electrospray ion source generating ions for analysis, the electrospray ion source comprising an exit port from which the ions are electrosprayed at atmosphere; a mass analyzer having an inlet port enclosed in a vacuum housing for receiving the ions to be analyzed; and a diverging conical duct electrode having an entrance aperture and an exit aperture, the exit aperture having an inner diameter larger than an inner diameter of the entrance aperture, the entrance aperture positioned proximate the exit port of the electrospray ion source for receiving the ions at atmosphere from the electrospray ion source, and wherein the exit aperture is enclosed in the vacuum housing and operatively coupled to the inlet port for transporting the ions from atmosphere to the mass analyzer under vacuum.

[0013] In another aspect, an ion transfer device for transferring ions emerging from an electrospray ion source, having an exit port for spraying the ions at atmosphere, to a vacuum chamber, includes an inner surface in the shape of a diverging conical duct. The ion transfer device has an entrance aperture for positioning proximate the exit port of the electrospray ion source, the entrance aperture receiving the electrosprayed ions from the exit port of the electrospray ion source at atmosphere. The diverging conical duct is an electrode toward which the ions migrate and has an exit aperture with an inner diameter larger than an inner diameter of the entrance aperture, the exit aperture configured to be operatively coupled to the vacuum chamber for transferring the ions thereto.

[0014] In addition to the above aspects of the present disclosure, additional aspects, objects, features and advantages will be apparent from the embodiments presented in the following description and in connection with the accompanying drawings.

BRIEF DESCRIPTION OF THE FIGURES

[0015] FIG. 1 is a schematic representation of a prior art mass spectrometer.

[0016] FIG. 2 is a schematic representation of a cross-section of an embodiment of an ion transfer device of the present disclosure.

[0017] FIG. 3 is a schematic representation of a cross-section of an embodiment of a system formed in accordance with the present disclosure for the analysis of the mass spectra of ions formed from molecules of interest.

[0018] FIG. 4 is a schematic representation of a cross-section of a measurement apparatus for measuring transmission efficiency and transmitted current through an electrode interface of electrosprayed ions between atmosphere and a vacuum chamber.

[0019] FIG. 5A is a perspective representation of an embodiment of an ion transfer device of the present disclosure.

[0020] FIG. 5B is a schematic representation of a cross-section of an embodiment of the ion transfer device of FIG. 5A.

[0021] FIG. 5C is a magnified view of the tip of the ion transfer device of FIG. 5B.

[0022] FIGS. 6A-6C are schematic representations of a cross-section of the measurement apparatus shown in FIG. 4, with three different electrode interfaces coupled to the vacuum chamber for measuring transmission efficiency and transmitted current through the different electrode interfaces to the vacuum chamber.

[0023] FIG. 7A is a graphical representation of the ion transmission through the ion transfer device of FIG. 5B compared to the ion transmission through various commercial capillary interfaces.

[0024] FIG. 7B is a graphical representation of a transmitted current through the ion transfer device of FIG. 5B compared to the ion current through various commercial capillary interfaces.

[0025] FIG. 8A is a graphical representation of an ion transmission through the slowest diverging conical duct portion of the ion transfer device of FIG. 5B compared to the ion transmission through capillary interfaces of varying lengths.

[0026] FIG. 8B is a graphical representation of the transmitted current through the slowest diverging conical duct portion of the ion transfer device of FIG. 5B compared to the ion transmission through capillary interfaces of varying lengths.

[0027] FIG. 9A is a graphical representation of the ion transmission through the ion transfer device of FIG. 5B compared to the ion transmission through various commercial rudimentary orifice interfaces.

[0028] FIG. 9B is a graphical representation of the transmitted current through the ion transfer device of FIG. 5B compared to the ion transmission through various commercial rudimentary orifice interfaces.

[0029] FIG. 10A is a schematic representation of the ion beam, and measured divergence of the beam, observed in the ion transfer device of FIG. 5B.

[0030] FIGS. 10B and 10C are schematic representations of the ion beams, and measured divergence of the beams, observed in the rudimentary orifice interfaces shown in FIGS. 6B and 6C, respectively.

[0031] FIG. 11 is a representation of a cross-section of another embodiment of an ion transfer device of the disclosure manufactured using electrical discharge machining (EDC).

[0032] FIG. 12A is a graphical representation of measurements of the electrosprayed current transmitted through a manufactured straight channel device.

[0033] FIGS. 12B-12E are graphical representations of measurements of the electrosprayed current transmitted through EDC-manufactured ion transfer devices of varying angles of divergence, formed in accordance with the present disclosure.

[0034] FIG. 13A is a graphical representation of the transmission efficiencies calculated from the measurements of FIGS. 12A-12E for the manufactured devices as compared to the straight channel device.

[0035] FIG. 13B is a bar graph representation of the average across the electrospray potential of each of the transmission efficiencies plotted in FIG. 13A.

[0036] FIG. 14 is a graphical representation of measured spot sizes formed a distance from the exit aperture for each of the EDC-manufactured ion transfer devices and for the straight-channel device.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0037] The following sections describe exemplary embodiments of the present disclosure. It should be apparent to those skilled in the art that the described embodiments of the present disclosure provided herein are illustrative only and not limiting, having been presented by way of example only. All features disclosed in this description may be replaced by alternative features serving the same or similar purpose, unless expressly stated otherwise. Therefore, numerous other embodiments of the modifications thereof are contemplated as falling within the scope of the present disclosure as defined herein and equivalents thereto.

[0038] The present disclosure is directed to a method and apparatus for improving the transfer of ions from the atmosphere into a vacuum of a mass spectrometer. The present disclosure is also directed to a mass spectrometer including the ion transfer apparatus of the disclosure.

[0039] Referring to FIG. 1, a prior art electrospray ionization mass spectrometer is described in co-owned U.S. 4,977,320 to Chowdhury, *et al.*, in which a long metal capillary tube 11 is used to couple the ionized spray emitted from an electrospray needle tip 14 at atmospheric pressure to a vacuum pressure chamber 21 in order to inject the ions into a mass analyzing chamber 31. The capillary tube 11 is also heated to preferably about 85 C to cause the ionized droplets and solvated ions to undergo continuous desolvation as they pass through the tube 11.

[0040] While the use of a heated capillary advantageously improved the ion desolvation process without the need for precise gas flow control, the efficiency of ion transmission into the vacuum chamber 21 using the capillary tube disclosed in Chowdhury is still low.

[0041] Referring to FIG. 2, the present inventors discovered that, surprisingly, a slowly diverging conical duct 52 provides a superior interface over the capillary tube of the prior art as an ion transfer device 50 for coupling electrosprayed ions from an electrospray source at atmosphere to a mass spectrometer at vacuum. In one embodiment of an ion transfer device formed in accordance with the present disclosure, about 75 to about 99 % of ions from a nano-flow ESI ion source placed a distance from an inlet port 25 of the device 50 can be transferred into vacuum through the ion transfer device 50, resulting in a total transmitted ion current of higher than 200nA from a nano-flow ESI source. This translates to an improved total transmitted current to a mass analyzer through the ion transfer device 50 from about 10 to about 100 times higher than can be achieved under similar conditions in commercial mass spectrometers that utilize a heated capillary as a key element of the interface.

[0042] Though not wishing to be bound by any particular theory, the inventors contemplate that the phenomenon of flow separation may be at least partially responsible for this surprising discovery of improved ion transmission through the slowly diverging conical duct of the present disclosure. It is surmised that the flow separation likely occurs when the gas/liquid moves in the diverging duct with a velocity higher than some critical velocity. The present inventors have demonstrated that an ion beam 54 produced from embodiments of the ion transfer device 50 has advantageous properties, including that: (i) it does not interact with inner walls 56 of the device 50 (presumably after flow separation takes place); and (ii) as the ion beam 54 propagates, it diverges very slowly. For example, measurements of a divergence of the ion beam 54 relative to a central longitudinal axis 58 of one embodiment of the diverging conical duct 52 were taken, showing a divergence angle of about 0.6 degrees. Such narrow ion beams can be efficiently heated, for example, by radiative heat from an encompassing heated sleeve, to provide ion desolvation.

[0043] In one embodiment of the present disclosure, the ion transfer device includes a diverging conical duct with an inner diameter of the inlet port between about 0.1-1 mm and an inner diameter of an exit port between about 0.2-5mm, an inner diameter of an exit port of the device being greater than the inner diameter of the inlet port.

[0044] Preferably, the inner diameter of the inlet port is from about 0.3mm to about 0.6 mm.

[0045] In another embodiment of the present disclosure, the ion transfer device includes a diverging conical duct with inner walls forming an angle of divergence 55 with the longitudinal axis 58 of the diverging conical duct 52 of from about 0.6 to about 1.0 degrees.

[0046] Preferably, the angle of divergence 55 is from about 0.7 degrees to about 0.9 degrees.

[0047] In other various embodiments, the angle of divergence 55 is less than about 1.0 degree and greater than about 0.6 degree and the inner diameter of the inlet port is about 0.4 mm.

[0048] In various preferred embodiments, the angle of divergence 55 is from about 0.75 degrees, preferably about 1.0 degree, to about 2.5 degrees.

[0049] In another preferred embodiment, the angle of divergence 55 is from about 1.0 degrees to about 2.0 degrees.

[0050] In yet another embodiment, the angle of divergence 55 is from about 1.0 degree to about 1.5 degrees.

[0051] In still other embodiments, the angle of divergence is from about 0.75 degrees, or from about 1.0 degree, to about 8 degrees.

[0052] In another embodiment, the angle of divergence is greater than about .1 degrees and less than about 10 degrees.

[0053] It should be apparent that the diverging duct or channel of the disclosure is configured and dimensioned such that the angle of divergence of the channel, while greater than zero, is sufficiently small to narrow an ion spray or beam that would otherwise be formed from the electrosprayed droplets passing through a simple aperture of the same diameter as the inlet port of the diverging duct.

[0054] In various additional embodiments of the present disclosure, a length of the diverging conical duct of the ion transfer device is from about 1 to about 200 mm. Preferably, the length is from about 5 to about 10mm.

[0055] In a preferred embodiment, an inner diameter of the inlet port is between about 0.3 mm and about 0.5mm, the angle of divergence 55 is between about 0.6 and about 0.9 degree, and the length of the diverging conical duct of the ion transfer device is at least about 7 mm.

[0056] The diverging conical duct of the ion transfer device is preferably maintained at a voltage of between about 0 and about 1000 V. The diverging conical duct is also preferably heated by any means known in the art to a temperature between about 273K and about 600K.

[0057] The diverging conical duct can be formed of any material appropriate for forming an electrode, which also conducts heat, including metals, conductive plastics, conductive glass, and so on. In a preferred embodiment the diverging conical duct is formed of conductive plastic.

[0058] Referring to FIG. 3, an embodiment of a system 100 for the analysis of the mass spectra of ions formed from molecules of interest includes the ion transfer device 50 of the present disclosure for coupling electrosprayed ions 40 from atmosphere to a mass spectrometer or analyzer 80 maintained in a vacuum housing 70. The electrosprayed ions 40 can be produced by introducing a dilute solution of the molecules of interest 30 into an inlet port 35 of the electrospray ion source 110. The ion source 110, which can be a nano-electrospray ion source, transports the dilute solution 30 and charges droplets of the solution to produce a divergent cone of electrosprayed ions 40 emitted from an exit port 45. A high voltage source maintains the ion source 110 at a high voltage relative to the

ion transfer device 50, preferably at about 1kV to about 2 kV. The system 100 also preferably includes a heating device 75 for heating the diverging conical duct 52 and a voltage source 155 for maintaining or altering a voltage applied to the diverging conical duct 52 of the ion transfer device 50, preferably between 0 and 400V. The diverging conical duct 52 forms an electrode, the voltage differential formed between the ion source 110 and the diverging conical duct 52 causing the charged droplets emitted from the ion source to migrate along electric field lines toward the entrance 25 of the diverging conical duct 52.

[0059] The mass analyzer 80 can be a quadrupole mass analyzer, like that shown in FIG. 1, an ion trap mass analyzer, a time-of-flight mass analyzer, or any mass analyzer known in the art.

[0060] In various embodiments of the system, the diverging conical duct 52 can be coupled to the front of the (first) vacuum stage of the mass spectrometer. In other embodiments, the diverging conical duct 52 can extend into the vacuum chamber.

[0061] In various embodiments of the system of the present disclosure, a gap 120 between the exit port 45 of the ion source 110 and an inlet port 25 of the ion transfer device 50 can preferably be varied as necessary to obtain optimum coupling efficiency of ions to the analyzer 80.

[0062] In one embodiment, a gap between the exit port 45 and the inlet port 25 is between about 10 mm and about 0.1mm. In another embodiment, the gap is less than about 4 mm.

[0063] In one preferred embodiment the ion source 110 is a nano-flow ESI.

[0064] In other embodiments, the nanoflow ion source can be coupled to the end of a liquid chromatography system, to a liquid pumping system, or simply to a tube containing the liquid to be electrosprayed.

[0065] Referring still to FIG. 3, the vacuum housing 70 can include a first vacuum chamber 72, to which an exit port 165 of the ion transfer device 50 is coupled, and a second vacuum chamber 74, as well as various elements including ion optics 76, such as

a skimmer, lenses, RF guides and so on between the exit port 65 of the ion transfer device 50 and a receiving port 75 of the analyzer 80.

[0066] Referring to FIG. 4, an experimental measurement apparatus 130 was assembled to compare an embodiment of the ion transfer device 50 of the present disclosure with other types of interfaces for coupling electrosprayed ions 132 from atmosphere to a vacuum chamber 134, representing a vacuum stage of a mass spectrometer. A Faraday cup 136 was positioned in place of an analyzer of a mass spectrometer for measuring the ion current transmitted (I_8). The ion source 138 for generating the ions 132 from a diluted sample 140 was a standard liquid junction nano-flow ESI ion source mounted on an x-y-z- stage. New Objective PicoTip capillary emitters having $10 \pm 1 \mu\text{m}$ pulled tip orifices (unless otherwise noted) were used for the nano-ESI ion source. For the high voltage supply 142, a Bertran supply was used. Two different solutions were electrosprayed: 60%/39%/1% MeOH/H₂O/acetic acid (from Fisher) and 0.1% v/w brilliant blue R dye (from Sigma-Aldrich) in 50/50 MeOH/H₂O. The solutions were introduced into the emitter 138 by a Harvard syringe pump with a flow rate of about 10 μl /hour. The x-y-z- stage was used to align the exit tip 144 of the emitter 138 relative to the entrance 146 of the particular atmosphere/vacuum interface under test, for optimizing alignment of the ESI-produced spray 132 of ions and droplets through each of the atmosphere/vacuum interfaces tested.

[0067] Referring to FIG. 5A, in one embodiment the diverging conical duct of an ion transfer device of the present disclosure is provided by a standard conductive plastic 0.3-10 μl pipette tip 150. A representation of a cross-section of one example of the pipette tip, exposing internal walls that form a slowly diverging conical duct, is provided in FIG. 5B.

[0068] The pipette tip 150 is made from conductive plastic, is about 30 mm long, and is available from Advion, 10 Brown Road, Suite 101, Ithaca, NY 14850 USA, as Part No. Catalog: CS109. The tip 150 contains a 7 mm-long section 160 of slowly diverging conical duct at its inlet tip 155, with an angle of divergence of about 0.8° . It was found that this section 160 alone can transmit ions better than any other type of electrode tested. The pipette 150 also contains additional diverging ducts with larger angles of divergence

that have an effect on ion transmission, improving the transmission further over the 7mm section alone. Referring to the circular inset 162 of FIG. 5B, the inner passage at the inlet 155 was additionally shaped (using a pin) to widen an inner diameter 164 at the inlet 155 of the ion transfer device to improve the suction flow of air into the diverging conical duct 152.

[0069] To compare the ion transmission through the conductive plastic tip 150, an embodiment of an ion transfer device of the present disclosure, with the transmission through other types of interfaces commonly used to transmit ions into a vacuum stage of a mass spectrometer, the conductive plastic tip 150 was replaced with different types of electrode interfaces and tested with the same apparatus 130. All of the electrodes were heated during the measurements. The electrode holder 60 was changed as needed to accommodate the different sizes of interfaces tested. Both custom-made capillaries having an Inner Diameter (ID) of about 0.5mm, Outer Diameter (OD) of about 1.64 mm, and length of about 5 to about 200 mm, and commercial capillaries taken from various commercial electrospray instruments (from LCQ, LTQ and Velos mass spectrometers, available from Thermo Fisher Scientific) were tested, including: a capillary from an LCQ-IT mass spectrometer (manufacturing year ~2000) with dimensions: ID ~ 0.5mm, OD ~1.56 mm, length ~184.4mm; a capillary from an LTQ-IT mass spectrometer (manufacturing year ~2005) with dimensions: ID ~0.5mm, OD ~1.56 mm, length ~101.7 mm; and a capillary from a Velos-IT mass spectrometer (manufacturing year ~2011) with dimensions: ID ~0.05mm, OD ~1.56 mm, length ~58.6 mm. A representative capillary 180 mounted with an electrode holder 62 to the vacuum chamber 134 is shown in FIG. 6A.

[0070] Referring to FIG. 6B, also tested was an electrode 190 from a commercial Synapt QqTOF mass spectrometer (available from Waters Corporation, 34 Maple Street, Milford, MA 01757), which has a ~0.3 mm diameter inlet orifice for accepting electrosprayed ions, followed by a short cone-shaped section that opens into a 8.3 mm ID tube for transferring the ions into the vacuum stage of a mass spectrometer. Referring to FIG. 6C, also measured was the ion transmission through a 0.5mm diameter hole in a flat electrode 200 of thickness 0.03mm. This electrode is a good example of the electrodes

used in rudimentary, orifice-type ion interfaces, as for example in the mass spectrometers manufactured by AB Sciex 71 Four Valley Drive, Concord, Ontario, L4K 4V8, Canada. In each case, an appropriate electrode holder 62, 64, 66 was used to couple the interface to the vacuum chamber 134, as shown in FIGS. 6A, 6B, and 6C, respectively.

[0071] To test the efficiency of ion transmission through the various interfaces into the vacuum chamber 134, the value of the emitted ion current 148 was measured (I_5 in FIGS. 6A-C; FIG. 4) from the nano-flow ESI ion source 138 and were compared with the current of ions that passed through the orifices or channels in the different electrodes as detected and measured (I_8 in FIGS. 6A-C; FIG. 4) by the Faraday cup 136.

[0072] The currents were measured with a picoammeter (Keithley, Model 480). The vacuum chamber 148 was evacuated with an Edwards 12 two-stage rotary pump with an effective speed of ~ 12.8 l/s (the nominal pumping speed of ~ 14.2 l/s was corrected for the experimentally measured conductance of the hose connecting the vacuum chamber 134 with the pump. The typical pressure in the chamber was in the range of about 3 - 8 Torr, depending on the geometry and type of electrode interface being measured.

[0073] The various metal capillaries 180 and the electrode holder 62 were heated by an electric heater to between about 80-200° C. The plastic tips can also be heated by heating an electrode holder (6), but the distribution of temperature along the tip was not measured.

[0074] Referring to FIGS. 7A, 7B, 9A and 9B, the ion transmission efficiency of the full conical duct was measured, as shown in FIG. 4, and compared with the measured transmission efficiency of a variety of metal capillaries collected from the different commercial mass spectrometers, as described above for the capillary 180 shown in FIG. 6A. Referring to FIGS. 8A and 8B, the ion transmission efficiency was also similarly measured for just the 7 mm front section of the pipette.

[0075] Referring to FIGS. 7A and 7B, the transmission efficiency 250 and absolute transmitted current 270 through the different types of capillaries and through an embodiment of the diverging conical duct of the present disclosure, based on the conductive plastic pipette 150 described above. The transmission efficiency 262 of the

conductive plastic pipette 150 was measured to be at least 5 times higher than that measured for the various capillaries tested 264 (Velos), 266 (LTQ), and 268 (LCQ), for voltages in a normal operating range of about 1200-1500 volts used for most typical nano-flow ESI liquid chromatography/mass spectrometry (LC/MS) experiments. As shown in FIG. 7B, the transmitted current was measured to be 10-100 times higher for the conical duct electrode 272 than that measured for the straight capillaries 274, 276, 278 in the same operating voltage range 279.

[0076] It is worth noting that at low electrospray voltages, around ~700 V, the transmission efficiency of the Velos-IT capillary 264 is almost as high as the transmission of the plastic tip 262 (~100%). This, perhaps, can be explained by a rather unidirectional “dripping” mode of electro-spraying at lower voltages. This tendency is quickly broken as the voltages are increased to the operating values between 1200 to 1500 volts needed to reach the “Cone-Jet” mode of spraying needed for robust performance of nano-flow ESI LC/MS experiments.

[0077] Referring to FIG. 8A and FIG. 8B, the transmission efficiency and absolute transmitted current were measured through 0.5-mm ID metal capillaries of varying lengths and compared to those measured for the 7-mm section 160 of the conductive plastic tip 150, which was cut from the end portion of the plastic pipette 150. This slowly diverging section 160 has a divergence angle of ~0.8°. The transmission efficiency 280 and the transmitted current 290 of this slowly diverging section 160 were measured to be at least 2 times higher than the transmission efficiency 282 and transmitted current 292 measured for the shortest metal capillary (5 mm), and even higher than those measured for an 11-mm long capillary 284, 294 and a 56-mm long capillary 286, 296 in the operating voltage range of 1200-1500 Volts 279. This result shows that the slowly diverging conical duct 160 at the tip of the full conical conductive pipette 150 plays an important role in maximizing the ion current transmitted.

[0078] Accordingly, the tendency of shortening metal capillaries to improve transmission was shown to have limited potential, in that the ion transmission efficiency and the total transmitted current increases rather slowly as the metal 0.5 mm ID capillary was

shortened from 56 mm (286, 296), down to 11 mm (284, 294), and then to 5 mm in length (282, 292) as shown in FIGS. 8A and 8B.

[0079] Referring to FIGS. 9A and 9B, the ion transmission efficiency 300 of the same slowly diverging conical section 160 of the plastic pipette 150 was found to be only slightly higher than that 302 of the electrode 190 (as shown in FIG. 6B), or than the transmission efficiency 304 through a rudimentary flat electrode 200 with a 0.5 mm orifice (as shown in FIG. 6C). However, under similar conditions, the transmitted current 306 for the slowly diverging conical section 160 was about 2 times higher than that 308, 310 measured through these other electrodes 190, 200 over the operating voltage range 279 of 1200-1500 Volts.

[0080] The higher ion transmission efficiency of the “orifice” type of interfaces (as compared to a capillary type) may stem from the very limited time for interaction of the ions with the walls of an orifice of the order of fraction of a 1 μ s. Beams formed by passing through capillaries, on the other hand, may spend 0.1-1 ms in the duct. The longer ion residence time in the capillaries have both positive and negative consequences. On the positive side, the long residence time in the heated capillary can ensure efficient desolvation of heavily solvated ions and small droplets by radiation heating. On the other hand, the longer opportunity for interaction of the beam with the capillary walls may lead to more substantial ion losses.

[0081] The proposed method of forming an ion beam in a slowly diverging conical duct in accordance with the present disclosure preferably accomplishes the following: (i) the beams formed in the diverging duct do not interact excessively with the inner walls, especially after flow separation takes place, and (ii) as the beam propagates it diverges very slowly. Referring to FIGS. 10A-10C, measurements were performed to characterize the ion beam that forms in the various electrode interfaces measured. Referring to FIG. 10A, the ion beam 320 that forms in the full-length conductive plastic duct 150 has a very small angle of divergence (α) of about 0.6 degrees. On the other hand, beams 322 and 324 (FIGS. 10B and 10C) formed by passing through the orifices of the commercial interfaces 190 and 200, shown in FIGS. 6B and 6C, diverge more quickly and are consequently much wider, with divergences, α , of about 1.8 degrees and 7 degrees,

respectively. Also importantly, the tightly focused beam 320 can travel a longer distance before the beam is dissipated by collisions with the residual buffer gas. Such a narrow beam can be efficiently heated by radiation, for example, emitted from an encompassing heated sleeve that is still large enough to prevent losses via interactions with the walls. Alternatively, the holder that couples the tip to the vacuum chamber can be heated.

[0082] The divergence of the beams 320, 322, and 324 formed in each of the interfaces were observed by electrospraying a solution of brilliant blue R dye through the different electrodes and allowing the ions and small droplets to interact with a 72 line/inch mesh (90% transmission) positioned at various distances from the entrances. The mesh was then removed and the picture of the spot formed by the beam was taken and analyzed for each electrode interface 150, 190, 200, respectively. The beam 320 formed in the diverging conical duct of the conductive tip 150 was measured to be about 3-10 times tighter than the beams formed in the other interface.

Example

[0083] We have discovered a way to increase the efficiency of ion transfer from atmosphere into vacuum to almost 100%. This high efficiency was achieved using a novel configuration for the electrode through which ions enter the mass spectrometer. We term this a "ConDuct" electrode because it contains a narrow, slowly diverging conical duct that is able to transmit a large ion current into the vacuum with minimal losses, surpassing performance of all other types of atmosphere vacuum interfaces that utilize orifices or heated metal capillaries. We have constructed a new atmosphere-vacuum ion transmission interface based on the ConDuct electrode and have demonstrated that it can transmit 100-to-1000 times more ions than a typical heated-capillary-skimmer based interface.

[0084] Method: We have modified an LCQ-DECAXP ion trap mass spectrometer (Thermo) by equipping the instrument with two atmosphere-vacuum interfaces that can operate simultaneously. One of these is the original interface of the mass spectrometer containing an 18cm-long heated metal capillary and a skimmer. The other interface contains a heated holder supporting the ConDuct electrode, a quadrupole ion guide and a

skimmer identical to that used in the first interface. Ions from both interfaces are mixed in a T-shaped quadrupole ion guide and transferred to the ion trap. To directly compare the relative ion transmission efficiencies, we used peptides labeled with heavy or light isotopes to distinguish between ions coming from the ConDuct interface and the original interface of the mass spectrometer.

[0085] Preliminary Data: Firstly, we found that a conductive plastic 0.1-10 μ l pipette tip can be used as one practical implementation of the ConDuct electrode. The tip contains a 7mm-long section of slowly diverging conical duct at its tip (the diameter of the entrance is ~ 0.4 mm), with an angle of divergence ~ 0.8 degrees.

[0086] Secondly, we showed that such a ConDuct electrode transmits 80-99% of the total ion current emitted from a typical nanospray ion source into the vacuum of the mass spectrometer, resulting in absolute transmitted currents > 200 nA. We determined that this total ion current was at least 10 times larger than the current transmitted through all the heated capillary geometries in current use and at least several times larger than through the orifice-type interfaces of even larger diameter.

[0087] Thirdly, we built a new atmosphere-vacuum interface based on the ConDuct electrode and demonstrated that it can transmit 100-to-1000 times more ions than a typical heated-capillary-skimmer based interface.

[0088] We also obtained some experimental evidence that supports our speculations that the phenomenon of flow separation is responsible for the improved ion transmission. Flow separation occurs when a gas moves in a diverging duct with a velocity higher than some critical velocity. We also demonstrated that the ion beam produced this way has the following advantageous properties: (i) it does not interact with the inner walls; and (ii) the beam diverges very slowly as it leaves the duct and propagates through the vacuum.

[0089] Our results encourage further exploration of the phenomena involved in the formation of molecular and ion beams as they move through the slow diverging conical ducts and utilization of these phenomena for designing and implementing new atmosphere-vacuum interfaces with increased ion transfer efficiencies into mass spectrometers.

Additional example and data

[0090] Using electrical discharge machining (EDC), a series of stainless steel electrodes were produced. Each electrode has a length 398 of 24 mm and a machined conical inner surface forming a duct or channel 402 that slowly diverges from an inlet to an exit port. Four electrodes were formed, each with a diverging duct or channel having a full angle of divergence of 1, 2, 3, and 5 degrees, respectively (i.e., with angles of divergence measured from the longitudinal axis of .5, 1, 1.5 and 2.5 degrees, respectively). Referring, for example, to FIG. 11, each machined electrode 400 includes a slowly divergent conical duct 402 through which ions enter at its narrowest end 404. FIG. 11 shows a cross-section of one such electrode with the angle of divergence 406 from the longitudinal axis of 1 degree.

[0091] For comparison, an additional electrode with comparable dimensions was also machined with a non-diverging (0 degrees divergence) inner channel or duct.

[0092] The ion transmission through each of these EDC manufactured electrodes was measured. Referring to FIGS. 12A-12E, the electrodes having channel divergence angles as small as .5 degree, as shown in FIG. 12B, can increase ion transmission through the electrode to close to 100%, as is shown by comparison of the transmitted current 408 to the total current 410. In comparison, as shown in FIG. 12A, the transmitted current 412 through the straight channel (no divergence) was measured to be significantly lower than the total current 414 across the measured electrospray potential (1000 to 2000 V). The resultant current lost 416 is also plotted in FIG. 12A for the straight channel, to emphasize the inefficient transfer of ions through these straight channel devices. In comparison, the current lost 418 in the .5 degree divergent duct as shown in FIG. 2B is minimal.

[0093] Similarly, for diverging ducts having angles of divergence of 1 degree, 1.5 degrees, and 2.5 degrees, respectively, FIGS. 12C, 12D and 12E plot the transmitted current 420, 426, and 432 against the total current 422, 428, and 434 as well as the resultant lost current 424, 430, and 436, respectively.

[0094] Plots of the ion transmissions calculated from the measured currents for each of the machined diverging duct electrodes are shown in FIG. 13A and compared to the ion transmission 438 through the straight channel device. As shown in FIG. 13A, the ion transmission 440 through the .5 degree divergent duct is 4-10 times higher than the ion transmission 438 of the comparable straight channel duct. The ion transmission 442, 444 and 446 for each of the 1, 1.5 and 2.5 degree divergent duct, respectively, is also plotted in FIG. 13A with similar high transmissions especially at the higher electrospray potentials.

[0095] The average current transmission across the measured electrospray potential was also calculated and plotted for comparison in the bar graph of FIG. 13B. The average transmission efficiency 448 for the straight channel is at least six times lower than the average transmission efficiency 450 of the smallest measured divergent duct having .5 degree angle of divergence from the longitudinal axis, and lower still than the average transmission efficiency 452, 454 and 456 of each of the 1, 1.5, and 2.5 degree divergent ducts, respectively, as shown in FIG. 13B.

Exit Beam Divergence Measurements

[0096] To further describe our early surprising observations that the beam exiting the slowly diverging ducts of our disclosure diverges very slowly as it leaves the duct and propagates through the vacuum, we performed the following measurements. The diameter of a spot formed by the ion beam at a measured distance from the exit aperture or port for each of the four EDC machined diverging ducts was measured. This was accomplished by electrospraying a solution of a fluorescent dye (SYPRO Ruby) and measuring the diameter of the spots (using a florescent scanner) left on the targets intercepting the beam at the different distances. In so doing, beam divergences smaller than a few milliradians could be measured.

[0097] Referring to FIG. 14, the dependence of the exit beam divergence on the angle of the diverging conical duct is demonstrated by plotting the measured spot diameter for each of the EDC machined diverging ducts at a distance of 80 mm. These measurements confirm our earlier observations that the divergent duct electrodes of the disclosure

produce highly focused, laser-like sharp ion beams that propagate long distances in vacuum without appreciable dispersion. Superior results were demonstrated for the 1 to 1.5 degree (from the longitudinal axis) divergent ducts.

[0098] It was further demonstrated that the tight gas-dynamic beams produced could focus 5-10 nm diameter gold clusters, which were electrosprayed from water/methanol solution, to such a tight beam that it ablated a hole through a 1-micron thick nickel foil placed in vacuum 8-10 cm downstream of the inlet electrode. Although the observed ablation speed was slow (it took 20-30 min to cut a 300 um diameter hole in the 1-micron thick nickel foil), this was achieved without application of any voltage to influence the ion motion in the gas dynamic beam.

[0099] The unique properties of the ions beams produced by the divergent duct electrodes could prove potentially valuable in the several areas of scientific research. One immediate application is the replacement of the straight metal capillaries currently used in electrospray atmosphere-to-vacuum interfaces for mass spectrometers, with heatable metal divergent duct electrodes of the current disclosure.

[00100] While the invention has been particularly shown and described with reference to specific embodiments, it should be apparent to those skilled in the art that the foregoing is illustrative only and not limiting, having been presented by way of example only. Various changes in form and detail may be made therein without departing from the spirit and scope of the invention. Therefore, numerous other embodiments are contemplated as falling within the scope of the present invention as defined by the accompanying claims and equivalents thereto.

What is claimed is:

1. A system for mass spectra analysis of ions, the system comprising;
an electrospray ion source generating ions for analysis, the electrospray ion source comprising an exit port from which the ions are electrosprayed at atmosphere;
a mass analyzer having an inlet port enclosed in a vacuum housing for receiving the ions to be analyzed; and
a diverging conical duct electrode having an entrance aperture and an exit aperture, the exit aperture having an inner diameter larger than an inner diameter of the entrance aperture, the entrance aperture positioned proximate the exit port of the electrospray ion source for receiving the ions at atmosphere from the electrospray ion source, and wherein the exit aperture is enclosed in the vacuum housing and operatively coupled to the inlet port for transporting the ions from atmosphere to the mass analyzer under vacuum.
2. The system of claim 1, wherein the electrospray ion source is a nano-flow electrospray ion source.
3. The system of claim 1, further comprising a voltage source for imposing a voltage of about 500V to about 5kV on the electrospray ion source.
4. The system of claim 1, further comprising a voltage source for imposing a voltage on the diverging conical duct electrode.
5. The system of claim 1, further comprising a heating source for heating the diverging conical duct electrode.
6. The system of claim 5, wherein the heating source provides radiative heat.
7. The system of claim 1, wherein the mass analyzer is a quadrupole mass analyzer.
8. The system of claim 1, wherein the vacuum housing encloses a first vacuum chamber and a second vacuum chamber, the first vacuum chamber enclosing the

exit aperture of the diverging conical duct electrode, the system further comprising a skimmer, the second vacuum chamber enclosing an outlet side of the skimmer and the inlet port of the mass analyzer, and wherein the second vacuum chamber is maintained at a greater vacuum than that of the first vacuum chamber.

9. The system of claim 1, wherein the diverging conical duct electrode has a diverging angle greater than 0.1 degrees and less than about 10 degrees.

10. The system of claim 10, wherein the diverging conical duct electrode has a length from about 1 mm to about 200 mm.

11. The system of claim 1, wherein the entrance aperture of the diverging conical duct electrode is positioned a distance of between about 0.1 mm and about 10 mm from the exit port of the electrospray ion source.

12. The system of claim 1, wherein an inner diameter of the entrance aperture of the diverging conical duct electrode is from about 0.1 mm to about 1 mm.

13. An ion transfer device for transferring ions emerging from an electrospray ion source to a vacuum chamber, the electrospray ion source having an exit port for spraying the ions at atmosphere, the ion transfer device comprising:

an inner surface in the shape of a diverging conical duct, the ion transfer device having an entrance aperture for positioning proximate the exit port of the electrospray ion source, the entrance aperture receiving the electrosprayed ions from the exit port of the electrospray ion source at atmosphere, the diverging conical duct being an electrode toward which the ions migrate and having an exit aperture with an inner diameter larger than an inner diameter of the entrance aperture, the exit aperture configured to be operatively coupled to the vacuum chamber for transferring the ions thereto.

14. The ion transfer device of claim 13, wherein the diverging conical duct has a diverging angle greater than 0.1 and less than about 10 degrees.

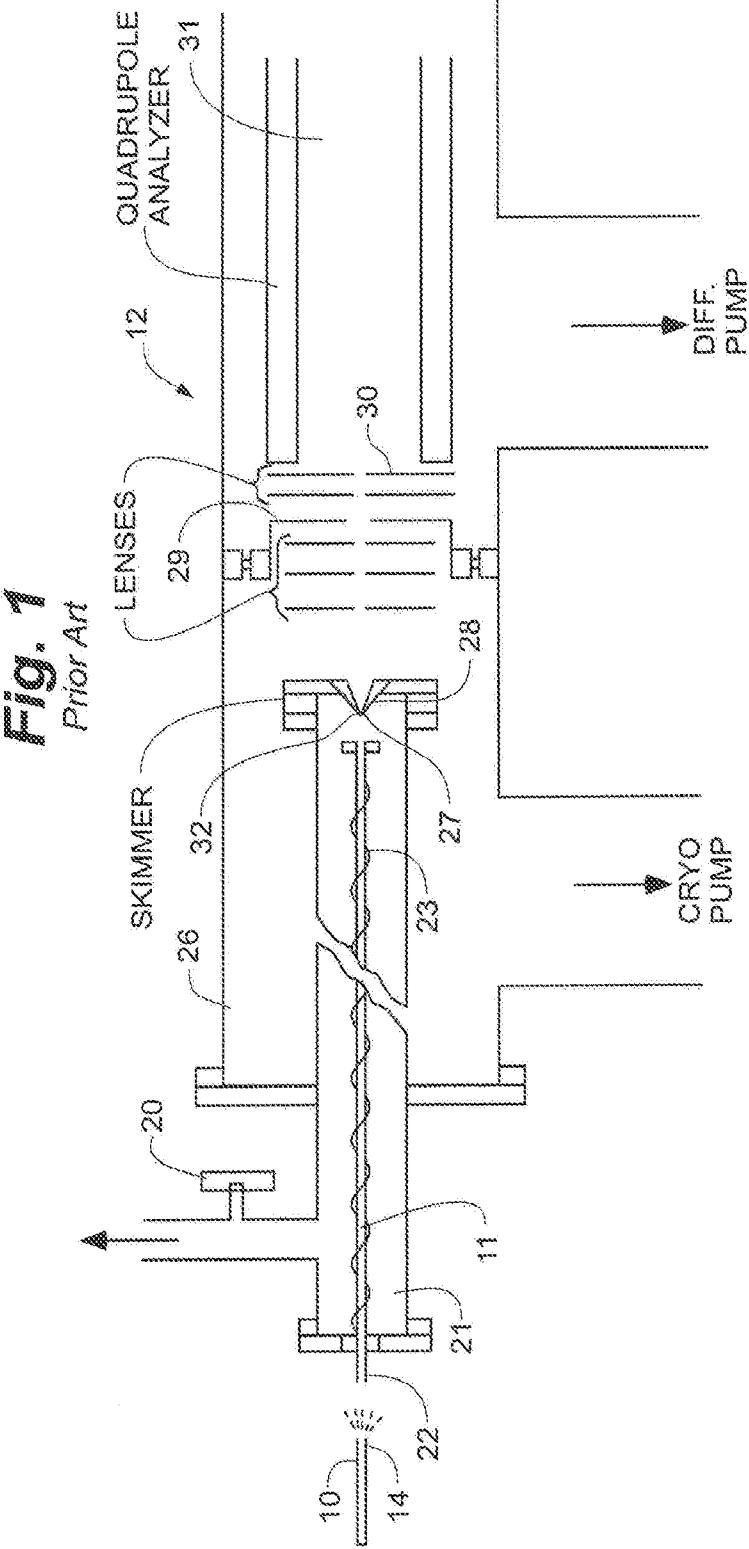
15. The ion transfer device of claim 13, wherein the diverging conical duct has a length of between about 1 mm and about 200 mm.

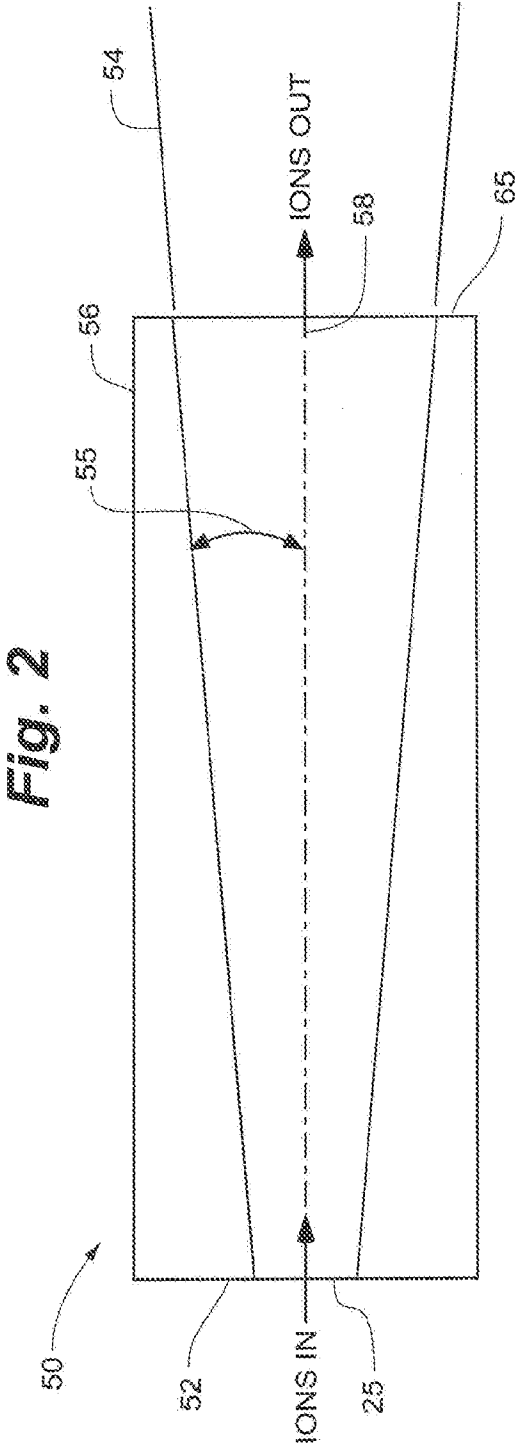
16. The ion transfer device of claim 13, wherein an inner diameter of the entrance aperture of the diverging conical duct is from about 0.1 mm to about 1 mm.

17. The ion transfer device of claim 13, further comprising a voltage source for imposing a voltage on the diverging conical duct.

18. The ion transfer device of claim 13, further comprising a heating source for heating the diverging conical duct.

19. The ion transfer device of claim 18, wherein the heating source provides radiative heat.





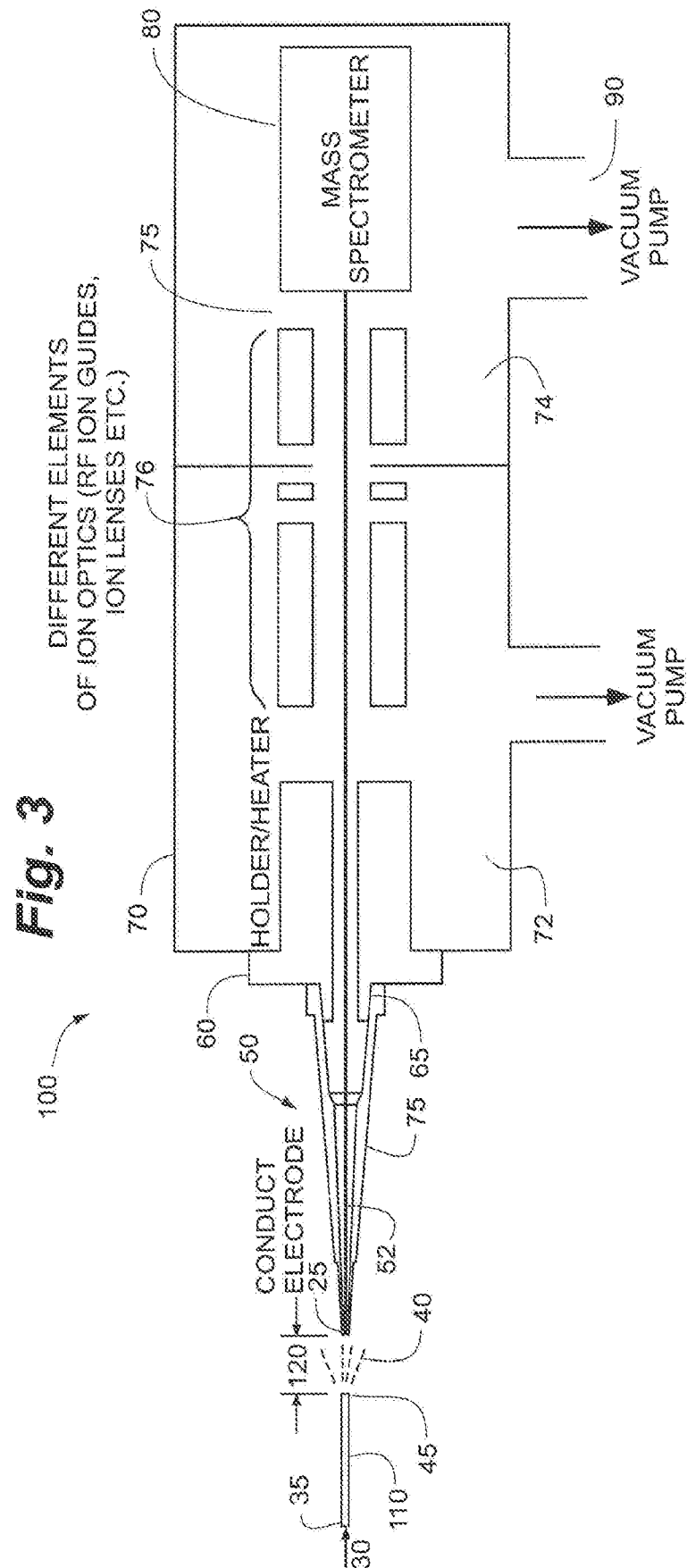
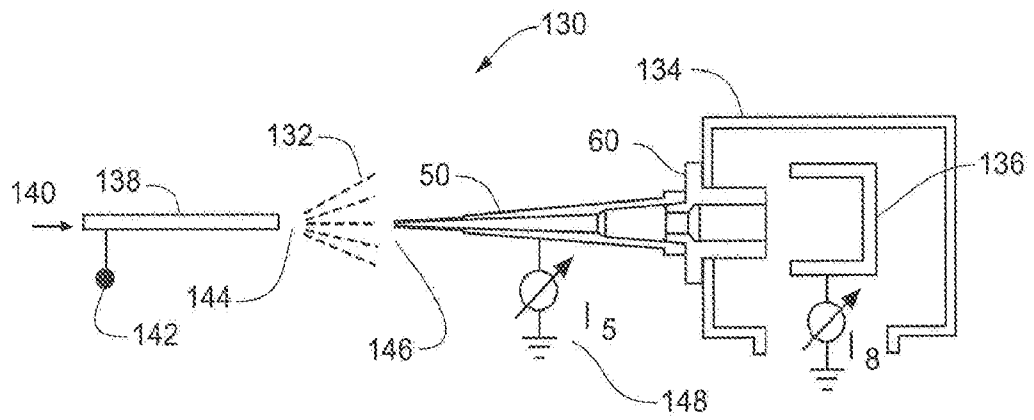
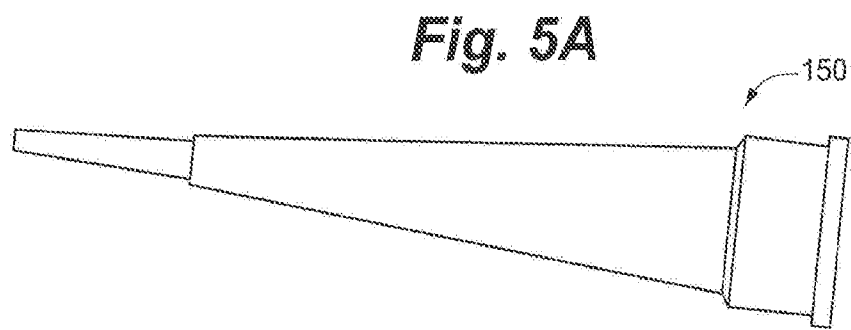


Fig. 4





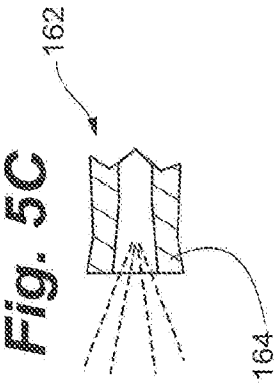
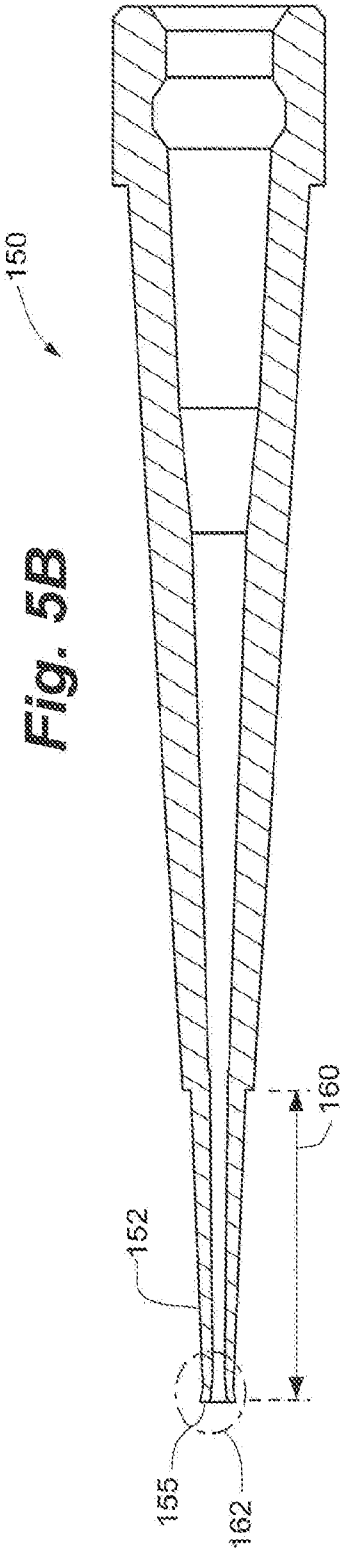


Fig. 6A

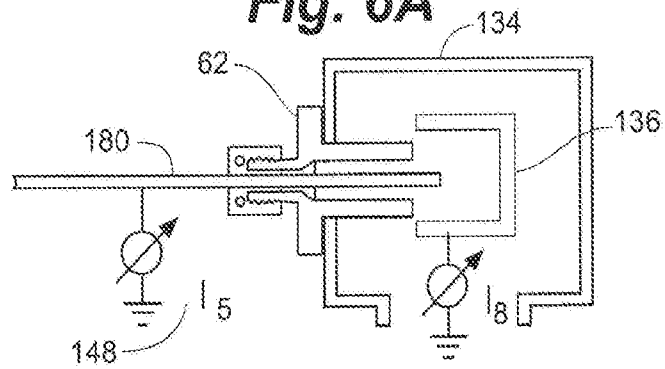


Fig. 6B

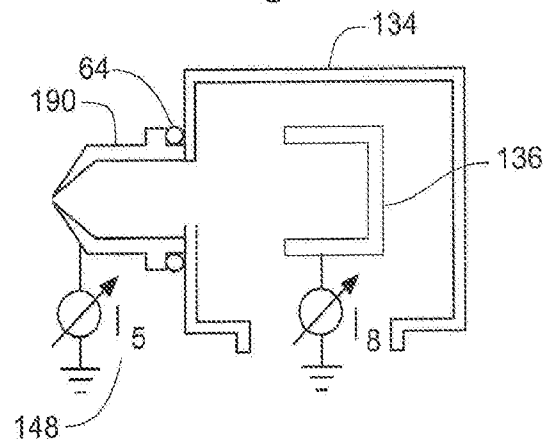
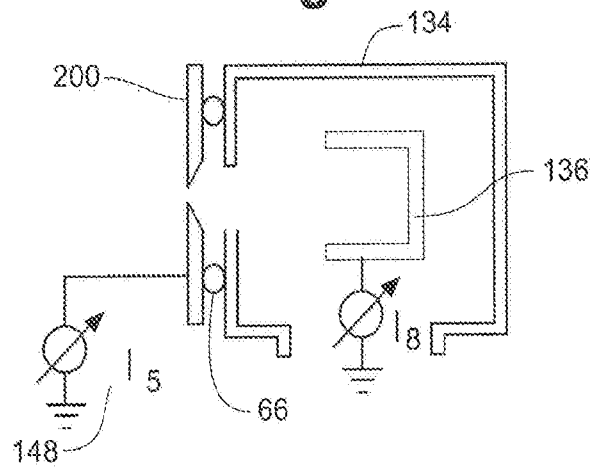


Fig. 6C



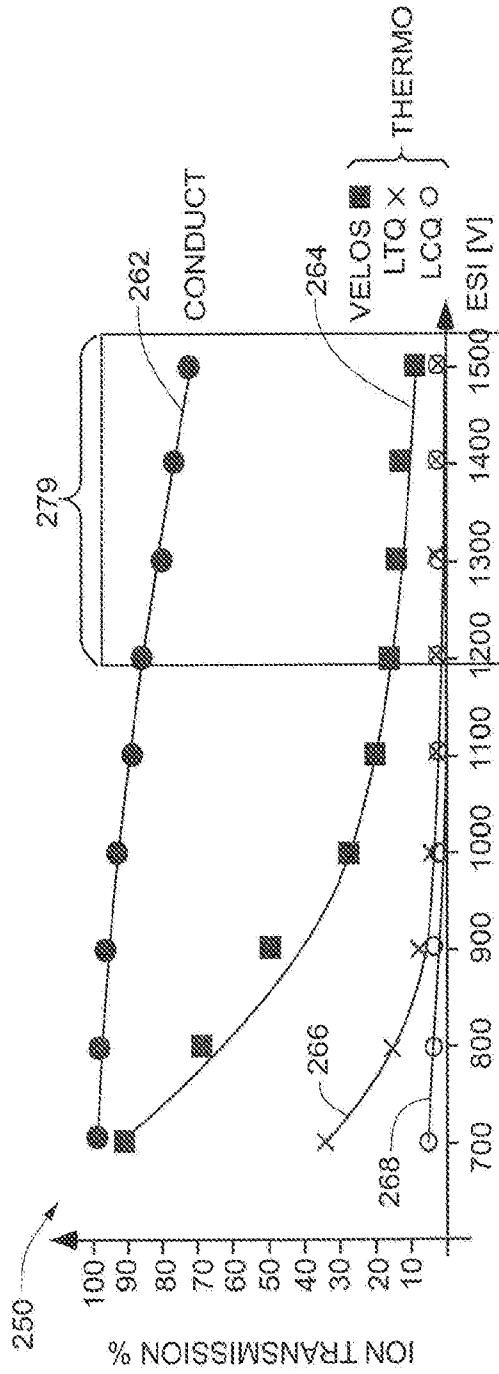


Fig. 7A

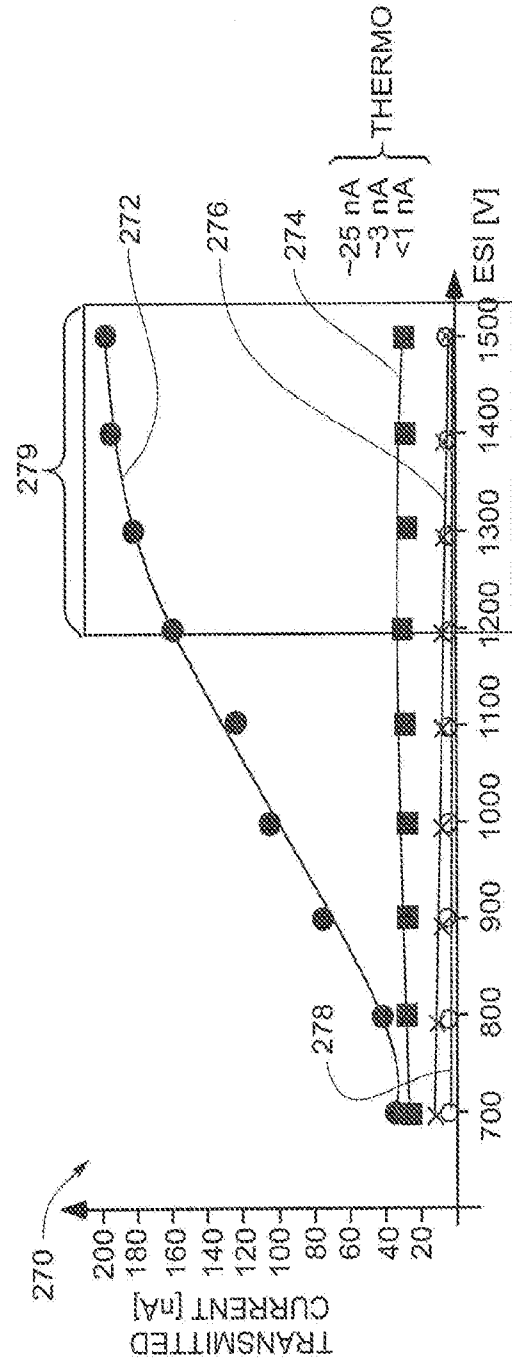


Fig. 7B

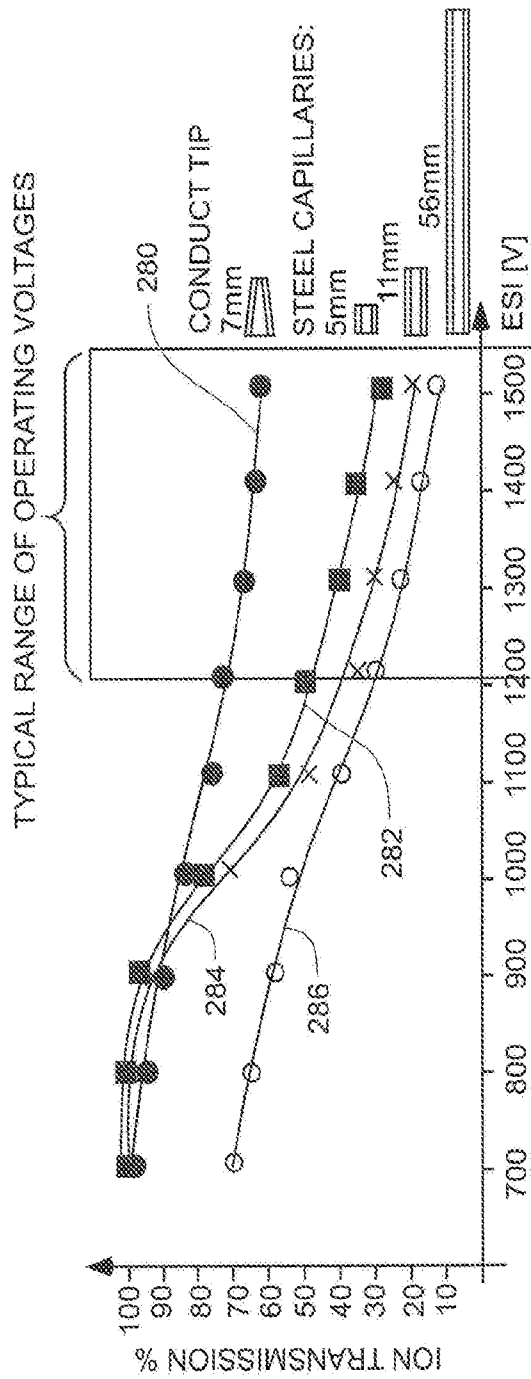


Fig. 8A

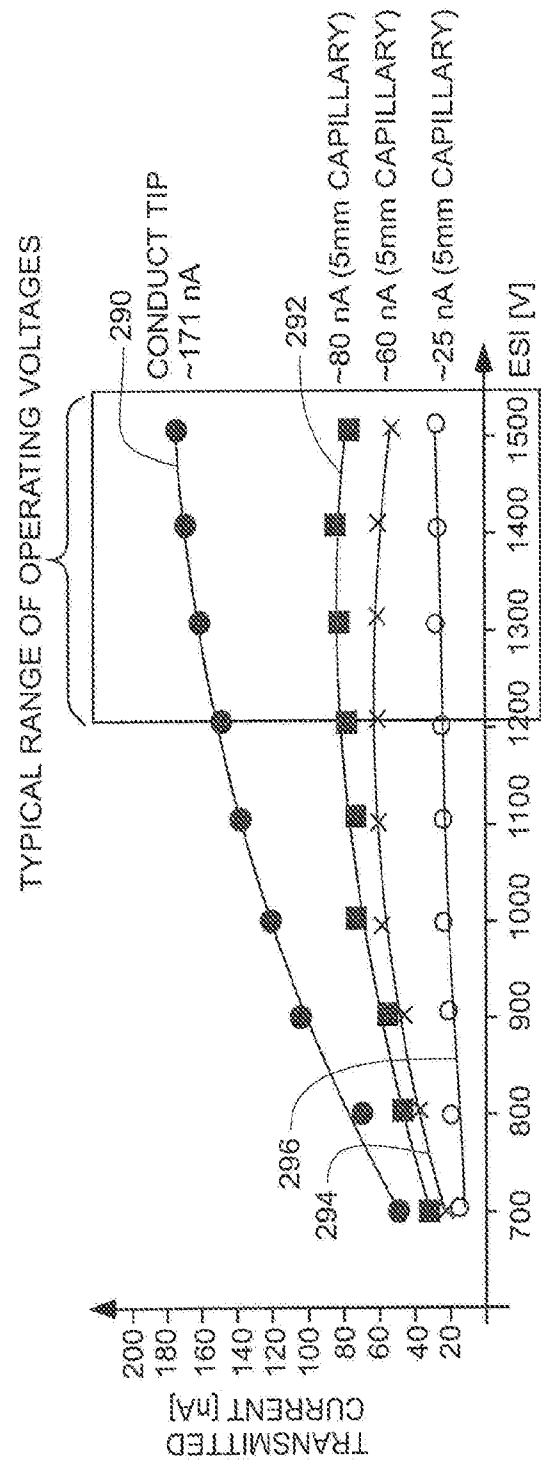


Fig. 8B

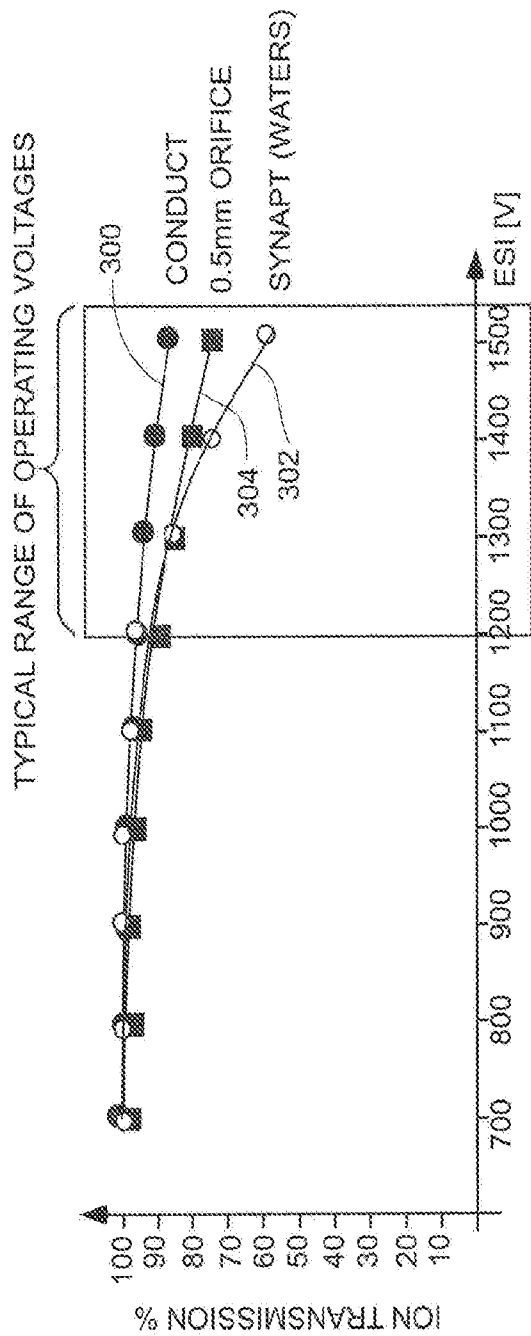


Fig. 9A

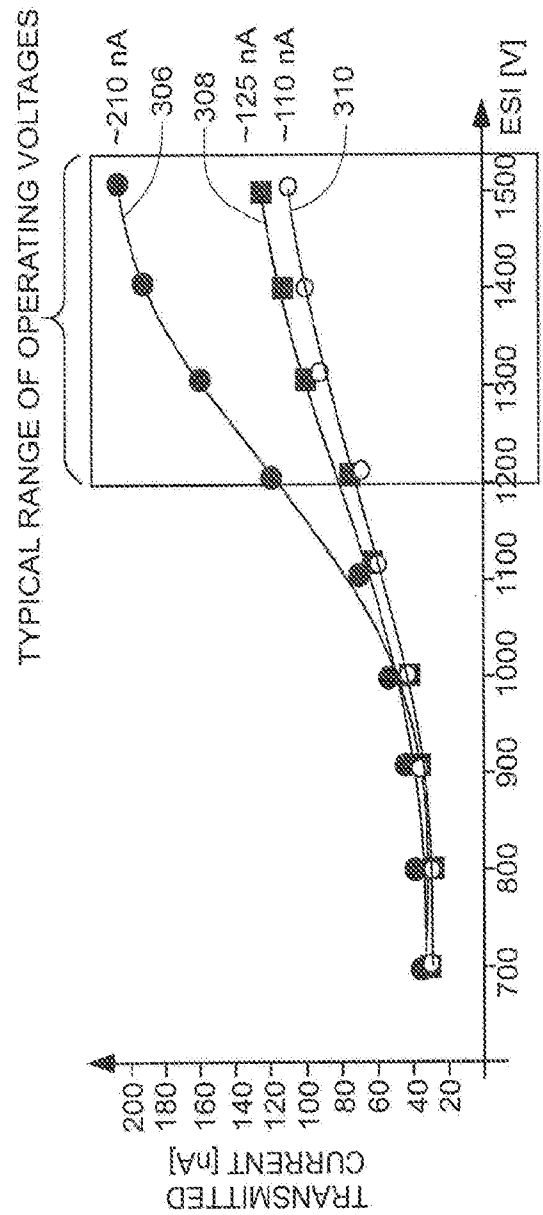
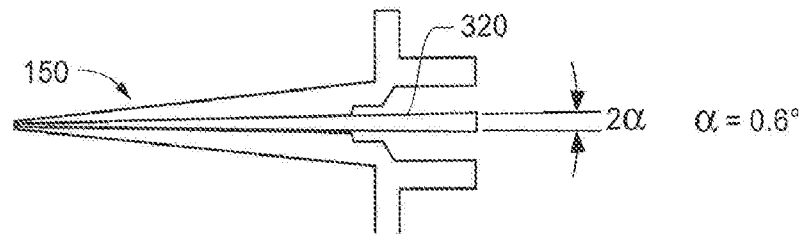
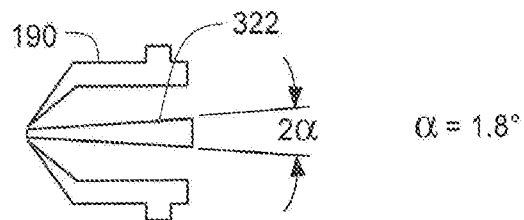
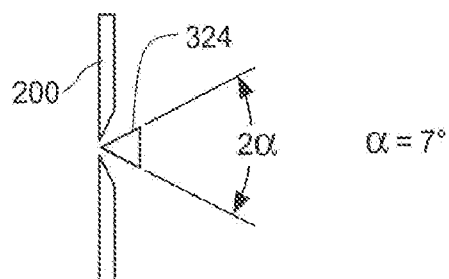


Fig. 9B

Fig. 10A**Fig. 10B****Fig. 10C**

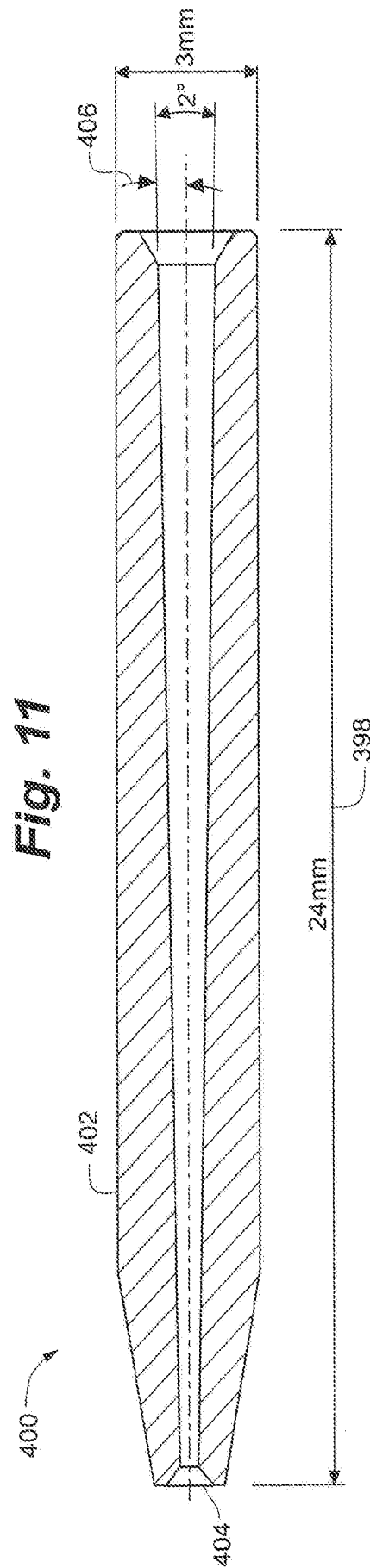


Fig. 12A

0°

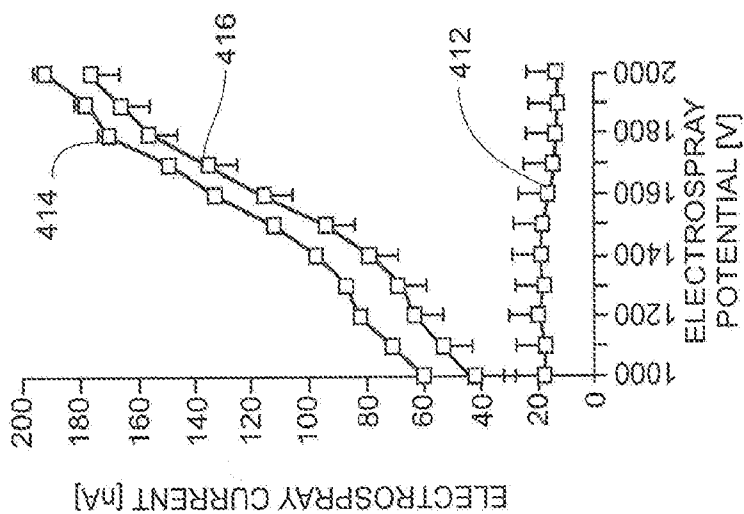


Fig. 12B

1°

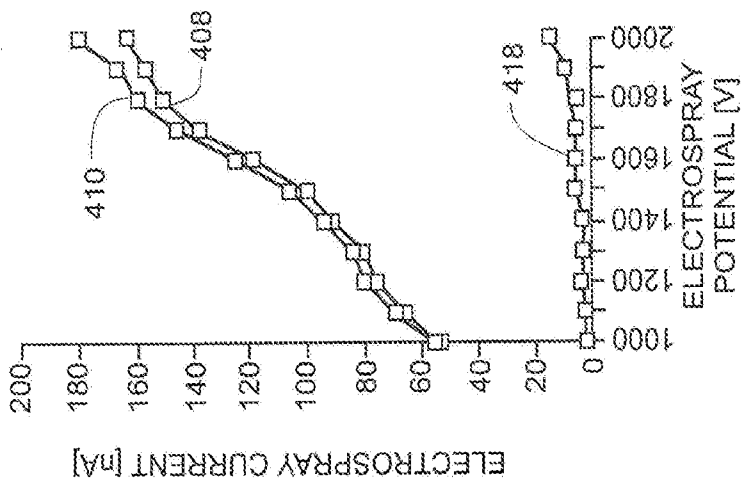


Fig. 12C

2°

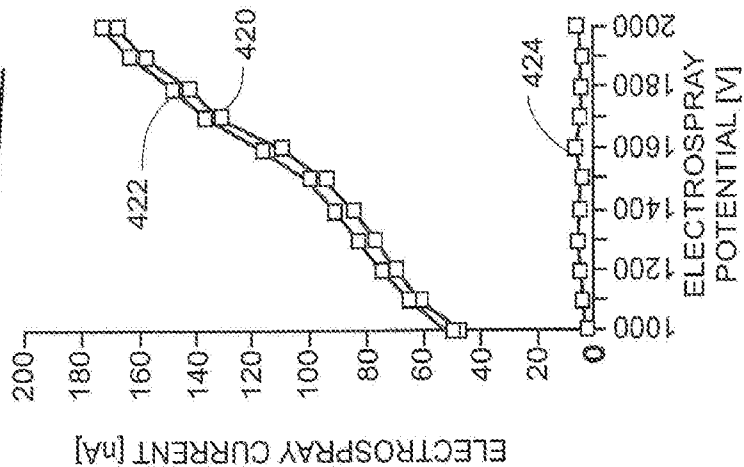


Fig. 12E

5°

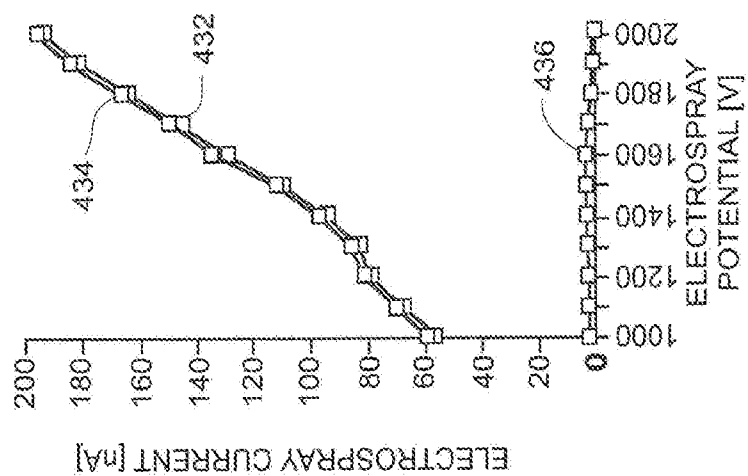


Fig. 12D

3°

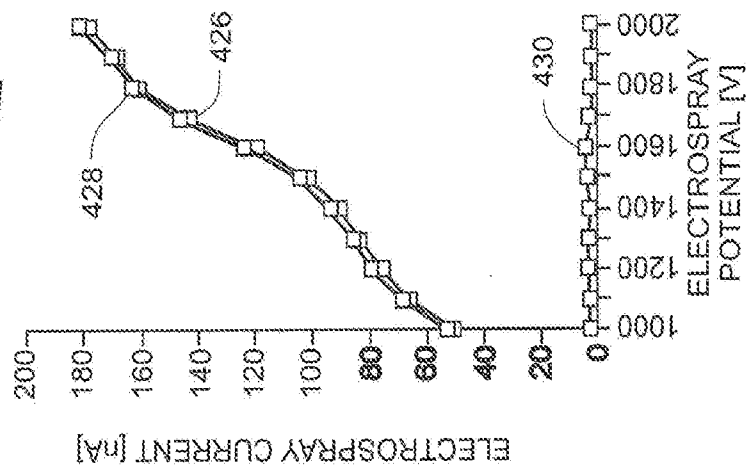


Fig. 13B

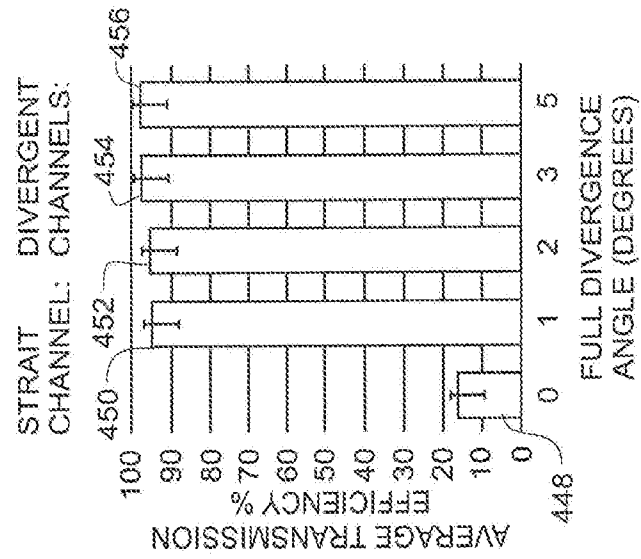


Fig. 13A

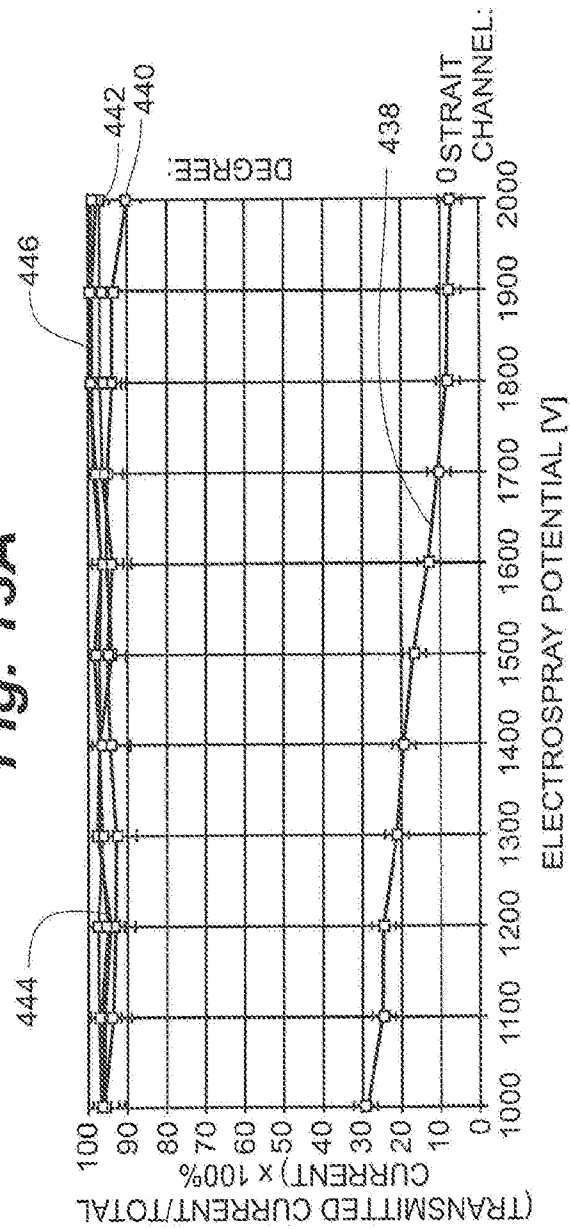
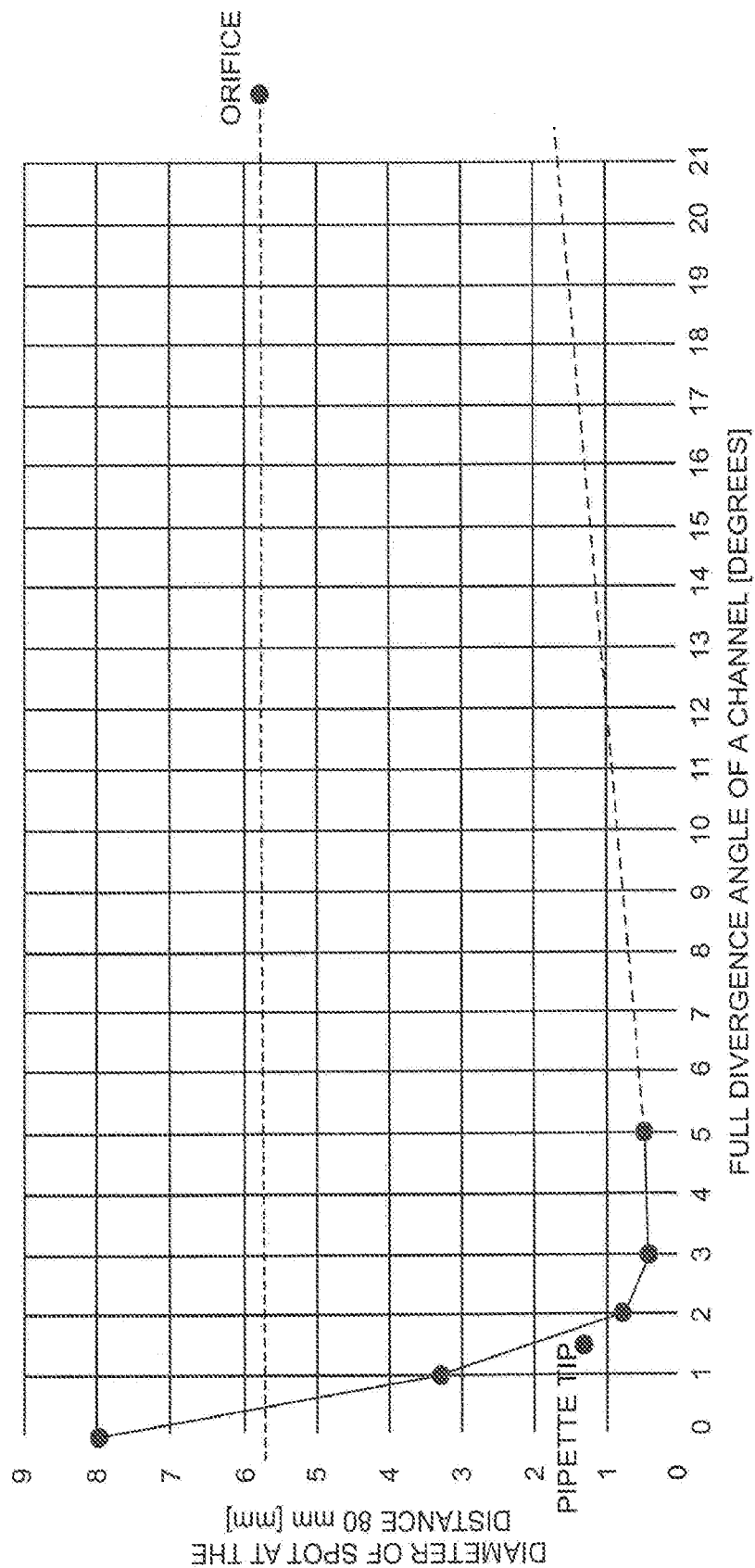


Fig. 14



INTERNATIONAL SEARCH REPORT

PCT/US14/14221

International application No.

PCT/US14/14221

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - H01J 49/04, 49/26; B05B 5/025 (2014.01)

USPC - 250/281, 423R; 239/690

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): H01J 49/04, 49/06, 49/10, 49/14, 49/26, 49/32; B05B 5/025, 5/035, 5/053, 5/16 (2014.01)

USPC: 250/281, 289, 294, 423R; 239/690, 692

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; ProQuest;

KEYWORDS: electrospray mass analyzer spectrometer ion aperture diameter radius cross sectional area voltage electrostatic heat vacuum chamber housing skinner conical diverging duct electrode

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,245,186 A (CHAIT, B. et al.) September 14, 1993; figures 1-4; column 2, line 55 to column 3, line 40; column 3, line 60 to column 6, line 48; claims 1, 4, 5, 11, 14 19 and 22.	1, 3-19
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Y		2
Y	US 5,788,166 A (VALASKOVIC, G. et al.) August 04, 1998; figure 3; column 4, lines 20-47.	2
A	US 4,977,320 A (CHOWDHURY, S. et al.) December 11, 1990; entire document.	1-19

☐ Further documents are listed in the continuation of Box C.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

06 May 2014 (06.05.2014)

Date of mailing of the international search report

20 MAY 2014

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