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(54) **HAND-HELD IONIZATION DEVICE FOR AMBIENT MASS SPECTROMETRY**

(57) The invention relates to a hand-held ionization device for ambient mass spectrometry comprising an outer housing (4), an ion transfer tube (3), an ion source comprising a first emitter (1) and a second emitter (2), preferably a camera module (5), and a separate control unit (6), wherein parts of the ion transfer tube (3) and the ion source are inside the outer housing (4), wherein the first emitter (1) comprises a plasma device, wherein the second emitter (2) comprises a sprayer device, wherein

the position of the parts of the ion transfer tube (3) and the ion sources (1, 2), which are inside the outer housing (4), is fixed, wherein the separate control unit (6) allows to switch between the ion sources. The invention also relates to a mass spectrometry system comprising an ion analysis instrument (7) and an inventive hand-held ionization device and a method for direct ambient mass spectrometry.

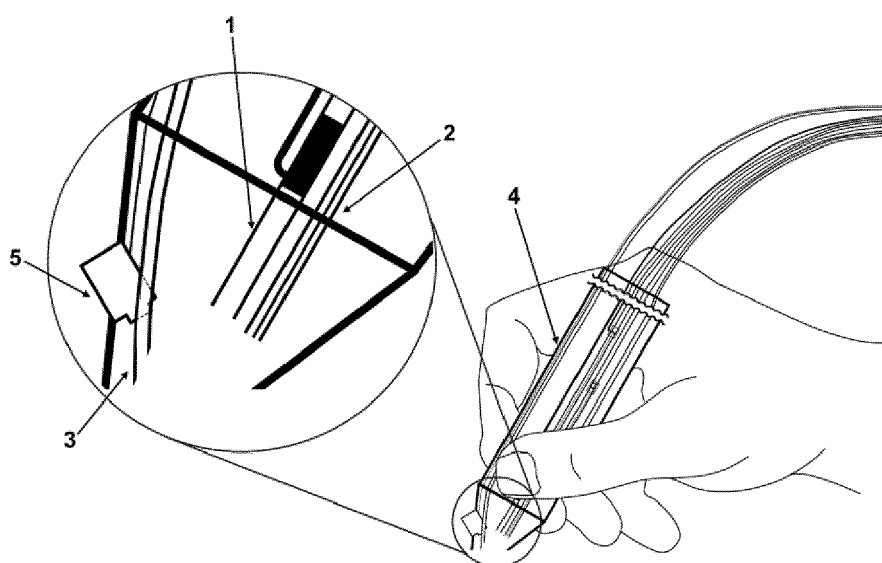


Fig. 2

Description

[0001] The invention relates to a hand-held ionization device for ambient mass spectrometry.

BACKGROUND OF THE INVENTION

[0002] In life and material sciences, the field of mass spectrometry has undoubtedly become an essential component of instrumental analysis with a wide range of applications. On the one side affordable, highly sensitive and accurate mass analyzers have been developed, on the other side the emergence of ambient mass spectrometry allows direct analysis of samples with no or little sample pretreatment in the open air.

[0003] Up to now a variety of both, direct as well as indirect surface sampling methodologies are available to ionize chemicals on surfaces at ambient conditions. The former include Desorption Electrospray Ionization (DESI), Easy Ambient Sonic-Spray Ionization (EASI), Direct Analysis in Real Time (DART), Low-Temperature Plasma (LTP) ionization, Rapid Evaporative Ionization Mass Spectrometry (REIMS), or Picosecond Infrared Laser Desorption (PIRL) with numerous important applications. A common feature of indirect surface sampling methods is the local separation of the extraction and the ionization process. Most common are Liquid Extraction Surface Analysis (LESA), Nanospray DESI (nano-DESI), commercially available Elution-based systems and, the recently launched MasSpec Pen.

[0004] The above-mentioned DESI is a liquid extraction technique, which encompasses a method that utilizes solvent to extract or desorb molecules from a sample surface. The majority of liquid extraction techniques utilize electrospray ionization as a means for ion generation. Thus, these liquid extraction techniques are typically used to analyze polar molecules that are more susceptible to ionization by electrospray ionization based mechanisms. For DESI, which is a spray-based extraction technique doing proton transfer through a droplet pick-up process, a voltage is utilized to generate an electrospray to extract and ionize analytes from a sample surface. More precisely, the primary DESI spray forms a thin film of solvent on the sample surface, from which secondary microdroplets containing the desorbed analytes are sequentially formed in a splashing process and propelled to the mass spectrometer for analysis. The resulting gas phase ions are commonly protonated/deprotonated molecules or often adducts with alkali, alkaline, or halogen ions. DESI has its unique advantage in the detection of large molecular weight compounds with low volatility.

[0005] A special mode of DESI where higher sheath gas flow rates and no voltages are applied to the spray solution is known as Easy Ambient Sonic-Spray Ionization (EASI). The EASI stream of bipolar (positively and negatively charged) droplets bombard a surface on which analytes are deposited, while droplet charging is sup-

posed to occur due to a static imbalance of charges within the sprayed droplets following the sonic spray mechanism. Main advantage of EASI over DESI is the total absence of high voltages, i.e. provided that a non-toxic spray solvent is used, human skin can safely be scanned using an EASI interface. Due to these facts the same spray-emitter can be utilized for DESI as well as for EASI.

[0006] Another possibility for ambient ionization mass spectrometry is given by the plasma desorption techniques. These techniques are derived from the same principles as atmospheric pressure chemical ionization, where plasma generated by a dielectric barrier discharge interacts with and ionizes volatile analyte molecules of interest through a series of ion-molecule reactions. The plasma desorption techniques utilize a similar process of plasma discharge to desorb and ionize molecules but are tailored for the direct analysis of unmodified samples. These methods can be used to ionize a variety of molecules in both the positive and negative ion mode. An example method which employs low-temperature plasmas for sample analysis is the above mentioned low-temperature plasma (LTP) ionization, which results in less sample damage and molecular fragmentation due to the low-temperature nature of the plasma. Beside desorption/ionization of low molecular weight compounds, low-temperature plasmas can also be utilized to specifically interact with C=C double bonds of targeted analyte molecules. Since Oxygen is ubiquitously present in the open air above the sample, minute amounts of ozone are formed in-situ due to ion-molecule reactions in the course of plasma formation. Ozone in turn readily reacts with and cleaves double bonds of analyte molecules via ozonolysis reaction, which can be exploited to e.g. localize double bonds in e.g. fatty acid side chains of lipids.

[0007] Summarizing, the plasma-based ion source and the electrospray-based ion sources are common desorption and ionization types for ambient mass spectrometry. Each of these three types of ion sources has their exclusive advantages as explained above.

[0008] However, the problem of providing a fast and easy to perform mass spectrometric analysis of a maximum variety of volatile as well as non-volatile chemicals on any kind of surface in the open air is up to now unsolved. The foundation stone for the solution of this problem is given by hand-held interfaces enabling a synchronous chemical and optical surface analysis. Most of the literature known systems of this kind have been designed for a potential medical use (avoiding extraction with organic solvents) like the above mentioned MasSpecPen disclosed in Zhang, J. et al.; Nondestructive tissue analysis for ex vivo and in vivo cancer diagnosis using a hand-held mass spectrometry system; Science translational medicine 2017, 9 (406), while others are limited in terms of their usability e.g. due to separated ion guide to mass spectrometer like the ambient ionization platform disclosed in W. Ai et al.; A Versatile Integrated Ambient Ionization Source Platform; J Am Soc Mass Spectrom. 2018

Jul;29(7): 1408-1415.

[0009] Furthermore, it is known that the range of analytes which can be ionized by a single ionization technique is always limited in terms of analyte mass as well as analyte polarity. Thus, the present invention's aim is to overcome these problems.

SHORT DESCRIPTION OF THE INVENTION

[0010] The purpose of the invention is to provide an ionization device, which is easy to handle and allows real-time chemical as well as optical analysis of surfaces. The chemical analysis features the detection of a broad range of analyte molecules at the same time, while the correlation with an optical analysis allows an immediate 2D localization and mapping of chemicals on any surface.

[0011] The solution to the above stated problem is given by a hand-held ionization device for ambient mass spectrometry comprising an outer housing, an ion transfer tube, an ion source comprising a first emitter and a second emitter and a separate control unit. The housing comprises a tube with a preferably transparent tapered tip, wherein parts of the ion transfer tube and the ion source are inside the outer housing. The first emitter comprises a plasma device, preferably a low-temperature plasma (LTP) device and the second emitter comprises a sprayer device, preferably a desorption electrospray ionization (DESI) as well as an easy ambient sonic-spray ionization (EASI) device. Furthermore, the position of the parts of the ion transfer tube and the ion sources, which are inside the outer housing, is fixed. The separate control unit allows to switch between the different ion sources.

[0012] The combination of three different ion sources allows enlarging the range of molecules, which can be analyzed. Especially the very complementary ionization methods, namely two certain liquid extraction techniques and a certain plasma desorption technique, allow for a very wide range of analyte molecules in terms of molecular weight and polarity. More precisely, LTP ionization allows identifying chemical compounds with a low molecular weight, which are volatile, nonpolar or polar. DESI and EASI, however, also allow detecting compounds with a high molecular weight, which are polar or ionic. A great advantage of EASI is the generation of ions in absence of high voltages facilitating a hazard-free application e.g. on human skin. The consecutive use of LTP and DESI/EASI allows in-situ modification of high molecular weight analytes by reactive species such as ozone followed by desorption/ionization using the liquid extraction based modes of the interface. Thus, the combination of these three techniques allows for a large range of molecular weight and polarity. Furthermore, DESI/EASI and LTP also have an excellent potential for miniaturization, which is why they are the perfect ionization techniques for a small hand-held device.

[0013] In a preferred embodiment the outer housing of the hand-held ionization device has the shape of a pen,

wherein the tapered tip of the pen is open. Thus, the small hand-held device can be very comfortably held in a single hand by a person who is using the inventive ionization device and it can be moved freely over any surface of interest. The pen-like shape with the open tip at the front of the device also allows to move the device exactly over a place on the sample surface, which has to be investigated.

[0014] In an especially preferred embodiment the hand-held ionization device includes a camera module, which is connected via a flexible cable to the embedded PC inside the separate control unit. The camera cable may run through the hand-held device. The camera module may be mounted to the tip of the hand-held ionization device. It allows both, capturing of bar or QR codes to identify ticketed samples as well as obtaining live images of the sample surface spot, which is bombarded with either plasma ions (LTP mode) or charged droplets (DESI/EASI modes). Furthermore, automated object tracking and the determination of the optical flow based on the obtained real-time images enables both, the stitching of an optical image (panorama) of the scanned surface as well as recording the motion of the hand-held interface relative to the sample surface. Thus, the correlation of optical data obtained by the camera module and chemical data obtained by mass analysis allows the visualization of the two-dimensional distribution of the analyte molecules on the sample surface.

[0015] Summarizing, the synchronous recording of optical and chemical data allows both, the real-time optical 2D mapping of the tip movement relative to the surface as well as the chemical analysis at any point, which is touched with the tip of the pen-like ionization device. Hence, chemicals on any kind of surface may be analyzed and neither photographic imaging, sample preparation nor a physical change of ionization devices at the mass spectrometer is longer necessary.

[0016] In another embodiment the hand-held ionization device may comprise an optical flow sensor known from optical mice. The image sensor featuring an embedded on-chip displacement processing may be mounted close to the open tip of the hand-held ionization device and is connected to the embedded PC inside the separate control unit. The sensor cable may run through the hand-held device. Data from the optical flow sensor allows obtaining relative movement of the hand-held ionization device on the surface of interest in real-time.

[0017] Preferably, the angle between the two parallel emitters inside the housing and the sample surface is between 45° and 65°. This angle is called the setup angle and could also be defined by the angle between an imaginary line perpendicular to the surface of interest and the hand-held ionization device, which is between 25° and 45°. The choice of this setup angle is in the case of the inventive ionization device not easy, as it has to work optimally for the different ionization methods as well as for the collection of the ionized molecules through the ion transfer tube. It turned out that an angle between the

housing and the sample surface of 45° to 65° is an optimal incident angle for the plasma jet from the first emitter as well as for the droplets, which are sprayed onto the sample surface by the second emitter. At the same time also the collection angle of the ion transfer tube is optimal in this case.

[0018] In a certain embodiment the ion transfer tube, the DESI/EASI-emitter and the LTP-emitter are paralleled along the longitudinal axis of the hand-held ionization device. Preferably, the distance between the ion transfer tube and the DESI/EASI-emitter is between 4 and 10 mm, the distance between the DESI/EASI-emitter and the LTP-emitter is between 1 and 4 mm and the distance between the ion transfer tube and the LTP-emitter is between 3 and 7 mm. The distances are chosen such that on the one hand an optimal ionization may be accomplished by the three different ion sources and on the other hand also the collection of the ionized molecules can be achieved optimally via the ion transfer tube. By choosing the above stated distances a very large range in terms of molecular weight is possible. Thus, it is possible to broaden the spectrum of detectable analyte molecules.

[0019] In another embodiment of the inventive hand-held ionization device the ion transfer tube consists of a flexible tube and may consist of any kind of flexible plastic tubing such as polyether ether ketone (PEEK), polyethylene (PE) or preferably fluorinated ethylene propylene (FEP). In total the ion transfer tube may be from 0.4 to 1 m long, which allows a very flexible movement of the hand-held device, which is connected to an ion analysis instrument via the ion transfer channel. The backend of the tube is connected to the ion analysis instrument to guide the ionized molecules safely to the ion analysis instrument. The frontend of the flexible tube has a specifically shaped tip to guide the ionized chemicals in an optimal way to the ion analysis instrument.

[0020] The first emitter, which can comprise an LTP-emitter, may include a glass capillary surrounded by an outer metal tape or metal wire electrode in the vicinity of the tip of the hand-held ionization device. The surrounding electrode is connected to a 2 to 5 kV_{pp} AC power supply within the separate control unit. To facilitate the formation of dielectric barrier discharge plasma with a 5 to 10 mm afterglow region an inner ground electrode, preferably another metal wire may run through the inside of the glass capillary. Preferably, the inner diameter (I.D.) of the glass capillary is between 0.4 and 1 mm, the outer diameter (O.D.) of the glass capillary is between 1 and 2 mm, and the outer diameter of the inner metal wire is between 50 and 150 μm. The inner electrode is connected to ground within the separate control unit. To sustain the discharge preferably helium gas at roughly 1 bar is supplied from the separate control unit through flexible tubing, which is connected to the glass capillary.

[0021] Furthermore, the second emitter, which can comprise the DESI/EASI ion source, may include an inner capillary, which is concentrically held inside an outer,

Y-shaped capillary. Preferably, both capillaries are fused silica or metal capillaries. The inner capillary is used for solvent transport and has an I.D. between 40 and 60 μm and an O.D. between 300 and 400 μm. The rear side of the inner capillary may be connected to flexible tubing from a syringe pump at the separate control unit. In DESI mode and in order to facilitate the generation of charged droplets, a switch inside the separate control unit connects the DC high voltage potential from the mass spectrometer to the metal hollow needle of the syringe at the separate control unit, which contains the spray solvent. The outer, Y-shaped capillary is utilized to pass a nebulizing gas, which preferably is nitrogen at a pressure of more than 2 bar for DESI and more than 4 bar for EASI mode. The Y-shaped capillary's I.D. is between 0.8 and 1.2 mm and the O.D. is between 1.3 and 2 mm. The ratios between nebulizing gas pressure, I.D. as well as O.D. of the inner capillary and the I.D. of the outer capillary are chosen in order to achieve optimum ionization efficiencies in DESI as well as EASI using a common emitter.

[0022] The invention concerns also a separate control unit preferably comprising an embedded single board computer, which is utilized for switching between the three ionization modes LTP, DESI and EASI, i.e. controlling the supply of gases, solvent and high voltage into the pen-like device. A miniature camera module may be mounted at the tapered tip of the pen-like device. Preferably, the camera module is connected to the separate control unit. Furthermore, the separate control unit may also be used to control two solenoid gas valves for Helium and Nitrogen supply as well as a high voltage relay to switch DC high voltage, which is drawn from the mass spectrometer.

[0023] In another embodiment the hand-held ionization device may comprise an additional tubing for suction-assisted extraction of aerosols from the cavity inside the tip of the hand-held ionization device. The tubing may run through the hand-held device and allows removing of possibly hazardous aerosols formed during desorption/ionization processes inside the tapered tip.

[0024] The invention concerns also a mass spectrometry system comprising an ion analysis instrument such as a mass spectrometer and a hand-held ionization device. Preferably, the ion transfer channel guides the ionized chemicals to the inlet of the ion analysis instrument.

[0025] The ion analysis instrument may be connected to the hand-held ionization device via a PTFE sleeve. The connection allows for an automatic change of settings in the ion analysis instrument when the ion source in the hand-held ionization device is changed via the separate control unit.

[0026] Moreover, the present invention also includes a method for direct ambient mass spectrometry, which uses the mass spectrometry system, wherein the hand-held ionization device can be moved freely over any sample surface. The ionization mode can be changed via the separate control unit and the ionized molecules from the sample surface are analyzed in real time by the ion anal-

ysis instrument. In a preferred embodiment the hand-held ionization device comprises a camera module, such that the device movement can be optically tracked.

[0027] In another embodiment the method includes a consecutive use of the LTP-emitter and the DESI- or EASI-emitter, wherein the LTP-emitter is used for an in-situ modification of the sample surface, wherein DESI- or EASI-emitter is used for ionizing the molecules on the modified sample surface. Since LTP is not able to desorb/ionize high molecular weight compounds such as lipids, a combination of LTP pretreatment and desorption/ionization using DESI or EASI therefore allow both, an in-situ modification by reactive species of the plasma as well as consecutive mass spectrometric analysis via DESI or EASI desorption/ionization.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

[0028] The foregoing and other objects, features and advantages of the invention will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

Fig. 1 shows a descriptive view of the inventive hand-held ionization device connected to both, its separate control unit as well as the mass spectrometer.

Fig. 2 shows a descriptive view of the inventive hand-held ionization device with a zoomed in view of the tip of the device.

Fig. 3 depicts the main part of the hand-held ionization device with the ion transfer tube, the first and second emitter as well as the camera module.

Fig. 4 shows a more detailed front view of the hand-held ionization device with the camera module.

Fig. 5 shows a screenshot from the main computer, where the OEM software of the mass spectrometer is running in the background.

Fig. 6A - 6F show mass spectra generated using either the LTP ion source (6A - 6C) or the DESI as well as the EASI ion source (6D - 6F).

Fig. 7A - 7B show mass spectra of food products using the LTP ion source (7A) or the DESI as well as the EASI ion source (7B).

Fig. 8 shows a mass spectrum of Limonene and its in-situ ozonolysis products obtained utilizing the LTP mode of the interface.

[0029] In Fig. 1 an illustrative example of the application of the hand-held ionization device is shown. The interface is connected to a mass spectrometer 7 as well

as to a separate control unit 6, which supplies gases, liquid, solvent as well as AC voltage, and may receive optical data from a camera module 5 (see Fig. 2). Flexible tubing and cables allow the interface to be freely moved over a surface of interest.

[0030] In Fig. 2 an illustrative example of the hand-held ionization device and a hand of a person holding the device is shown, in order to present the small size of the device. The device comprises an outer housing 4, which has preferably a pen-shaped form with a tapered tip. As can be easily seen in the zoomed in view of the tip of the pen-shaped ionization device there are three tubes running through the device (1, 2 and 3). Certainly, the tip of the outer housing 4 has to be open, such that the plasma of the LTP or the solvent droplets of the DESI/EASI can reach the sample surface and the ion transfer tube can guide the ionized chemicals to the ion analysis instrument 7. Moreover, a camera module 5 may be mounted near the tip of the pen-like device, which is focused onto the spot of desorption/ionization on the surface of interest.

[0031] In the example in Fig. 2 the left tube is the ion transfer tube 3, which is preferably flexible and connected to an ion analysis instrument like a mass spectrometer 7. As one can see in the zoomed in view of the device's tip in Fig. 2 the ion transfer tube 3 is located as close as possible to the open end of the tip, such that it can effectively collect the ionized droplets from any surface.

[0032] The middle tube in Fig. 2 is the first emitter 1. This first emitter 1 preferably corresponds to a LTP-emitter. The low-temperature plasma extends out of the tube 1 and is used to desorb, ionize or chemically modify analytes on the sample surface. The plasma may be generated by dielectric barrier discharge (DBD). A discharge gas at a low flow rate and a high-voltage AC are used to sustain the plasma in an ambient environment. The temperature of the plasma torch can be adjusted over a wide range and can be as low as 30 °C. This allows avoiding damage of the sample substrates.

[0033] The two concentric tubes on the right in Fig. 2 represent the second emitter 2. In a preferred embodiment this second emitter 2 corresponds to a DESI/EASI-emitter. As the ionization is in this case accomplished via a liquid extraction/ionization technique, the right outer tube allows delivering nebulizing gas, while the inner tube is utilized to transport solvent to a sample surface. For DESI and EASI, which are spray-based techniques, plumes of droplets are generated at the tip of the inner tube and directed onto the surface with the help of the nebulizing gas delivered in the outer tube. This plume of droplets allows to desorb/ionize molecules from the sample surface, which can then be analyzed by a mass spectrometer 7.

[0034] The mini camera module 5 is preferably mounted in extension of the user's forefinger at the tapered tip of the pen-like device. This dorsal arrangement guarantees an optimum visibility onto the probe tip when a surface is scanned.

[0035] In Fig. 3 the inventive hand-held ionization de-

vice is depicted in more detail. Especially, the distances between the three main tubes inside the device are shown. Preferably, the distance d_1 between the ion transfer tube 3 and the first emitter 1 is between 3 and 7 mm, the distance d_2 between the first emitter 1 and the second emitter 2 is between 1 and 4 mm and the distance d_3 between the ion transfer tube 3 and the second emitter 2 is between 4 and 10 mm.

[0036] Furthermore, as can be seen in Fig. 3, the angle α between the tip of the hand-held device and the sample surface may be an acute angle. Preferably, the angle α is between 45° and 65° . The setup angle can also be defined by the angle γ , which is the angle between an imaginary line perpendicular to the sample surface and the hand-held ionization device. Hence, the angle γ may be between 25° and 45° . The setup angle is achieved by shaping the outer housing 4 of the device accordingly. More precisely, the tapered tip of the pen-like device is designed to achieve this setup angle when moving the device over a surface of interest.

[0037] Fig. 4 shows a more detailed sectioning of the single parts of the three tubes in the inventive hand-held device. More precisely, in the illustrative example in Fig. 4 the ion transfer tube *a* is a flexible tube which consists of any kind of flexible plastic tubing like polyether ether ketone (PEEK), polyethylene (PE) or preferably of fluorinated ethylene propylene (FEP). In a preferred embodiment the frontend of the ion transfer tube has a specifically shaped tip to enhance both, the collection of gaseous charged droplets as well as ionized chemicals. The backend of the ion transfer tube *a* in Fig. 4 is connected to the ion analysis instrument 7. The length of the whole ion transfer tube *a* may be around 0.6 m. The length may vary depending on the distance of the hand-held device to the mass spectrometer 7, which is connected to the inventive device via the ion transfer tube 3 and can be chosen as needed depending on the specific application. The inner diameter of the ion transfer tube *a* may be between 0.6 and 1 mm, and the outer diameter may be between 1.3 and 2 mm.

[0038] The first emitter 1, which corresponds to the middle tube in Fig. 4, comprises in this example embodiment a front part *b* and a back part *h*, a power supply *f* and a grounding cable *g*.

[0039] In a preferred embodiment the first emitter 1 presents an LTP-emitter. In this case the front part of the first emitter *b* may be a glass capillary with a preferred outer diameter of 1 to 2 mm and an inner diameter of 0.4 to 1 mm. The glass capillary acts as a dielectric barrier. In the preferred embodiment as shown in Fig. 4 the lower part of the glass capillary *b* in the vicinity of the tip of the hand-held device is surrounded by a metal tape or a metal wire corresponding to the outer electrode *c*. The outer electrode *c* is connected via cable *f* to a 2 to 5 kV_{pp} AC power supply located in the separate control unit 6. Above the outer electrode *c* and inside the glass capillary *b* a wire, preferably a metal wire, is used as the grounding inner electrode *d*. This inner electrode *d* may have an

outer diameter of around 100 μm . At the connecting sleeve *e* both, the extension of the ground electrode *g* is led through as well as the glass capillary is connected to flexible tubing *h*. This back part *h* corresponds to the helium gas entrance in the embodiment depicted in Fig. 4. Preferably, it is made of polyethylene (PE) or any other kind of plastic tubing and the gas stream pressure may range from 0.8 to 1.2 bar. The inner and outer diameter may be roughly the same as for the additional tube *o* in the second emitter. The discharge gas helium passes then through the glass capillary *b* to generate the low-temperature plasma. More precisely, the carrier gas stream forces the plasma to extend beyond the pair of electrodes and out of the capillary to make a plasma jet. Both, the grounding cable *g* as well as the flexible tubing *h* are connected to the separate control unit 6.

[0040] In a certain embodiment the length of the glass capillary may vary from 7 to 10 cm, the outer electrode *c* may have a width between 0.5 and 3 cm, the inner electrode *d* may be between 3 and 7 cm long.

[0041] The second emitter 2, which corresponds to the right tube in Fig. 4, comprises in this example embodiment the front parts *i* and *j*, the back parts *m* and *o* and the junctions *k*, *l* and *n*. In a preferred embodiment the second emitter 2 presents a DESI/EASI-emitter.

[0042] The front parts *i* and *j* of the second emitter constitute the sprayer of the second emitter 2, which in the preferred embodiment in Fig. 4 correspond to a combined DESI/EASI-emitter. The front parts *i* and *j* may be concentrically arranged capillaries. The front part *i* of the sprayer may be a Y-shaped metal capillary with an preferred inner diameter between 0.8 and 1.2 mm and an preferred outer diameter between 1.3 and 2 mm. The front part *j* of the sprayer is preferably made out of fused silica and may have an inner diameter roughly around 50 μm and an outer diameter roughly around 360 μm , whereas in the embodiment as depicted in Fig. 4 the length of the front part *i* is between 4 and 6 cm and the length of the inner fused silica capillary *j* is between 5 and 6 cm. The fused silica capillary *j* is held in place by a tightly fitted PTFE tubing *k*.

[0043] The back part *m* comprises flexible tubing to transport solvent to the sprayer of the second emitter 2. Back part *m* is connected to the left arm of *i* with the help of a junction *l*, which is preferably PTFE tubing. In a preferred embodiment this back part *m* is consisting of polyethylene (PE) or any other kind of plastic tubing connected to solvent delivering syringe at top of the separate control unit 6. The flow rate of the syringe pump at the separate control unit 6 is preferably ranging from 10 to 40 $\mu\text{L}/\text{min}$.

[0044] The back part *o* comprises flexible tubing to transport nebulizing gas to the sprayer of the second emitter 2. Back part *o* is connected to the right arm of *i* with the help of a junction *n*, which is preferably PTFE tubing. In a preferred embodiment this back part *o* is consisting of polyethylene (PE) or any other kind of plastic tubing connected to the separate control unit. The pre-

ferred nebulizing gas pressure of this gas stream is ranging from >2 bar for DESI and >4 bar for EASI mode. The nebulizing gas preferably is nitrogen, which allows generating highly charged, primary solvent droplets.

[0045] In a preferred embodiment the source for a high voltage DC potential to perform DESI is the mass spectrometer 7. Preferably, the DC potential provided by the mass spectrometer 7 is around 4 to 5 kV and it is applied to the spray solvent via the metal hollow needle of the syringe, which is used to deliver the solvent from the separate control unit 6. In EASI mode, a switch inside the control unit 6 electrically disconnects the DC high voltage potential from the metal hollow needle of the solvent containing syringe.

[0046] Moreover, the exemplary embodiment of the inventive hand-held ionization device utilizes a camera 5. Preferably, this camera 5 is dorsally arranged at the tip of the hand-held device. It may be arranged close to the ion transfer tube 3. A camera cable q may also be connected with the camera 5 and run through the hand-held device to the separate control unit 6.

[0047] The invention concerns also a separate control unit 6 comprising an embedded single board computer, preferably a Raspberry Pi 4 (Model B) with a 1.5 GHz 64-bit quad core ARM Cortex-A72 processing unit and 4 GB random-access memory, which is utilized for switching between the three ionization modes LTP, DESI and EASI, i.e. controlling the supply of gases, solvent and high voltage into the pen-like device. A miniature camera module 5, preferably a Raspberry Pi (Type OV5647) camera with a 5 MegaPixel sensor and 70° degree field of view in length of 30 cm, which is mounted at the tapered tip of the pen-like device may be connected to the 15 pin Camera Slot Interface (CSI) of the Raspberry Pi 4. Furthermore, a Sseed Relay Board v1.0 for Raspberry Pi may be used to control two solenoid gas valves for Helium and Nitrogen supply as well as a high voltage relay to switch DC high voltage, which is drawn from the mass spectrometer 7.

[0048] In Fig. 5 a screenshot of the graphical user interface (GUI) of the OEM software of the mass spectrometer is shown. Two additional windows are opened in the screenshot, one shows the video stream, the other control buttons to switch in between the three different ionization modes and turn off the interface. With the help of these GUIs an user can very easily operate the inventive hand-held ionization device.

EXAMPLES

[0049] For the direct chemical analysis with the inventive hand-held ionization device the flexible ion guide tube is connected to the heated capillary of a LTQ-Orbitrap XL mass spectrometer (Thermo Fisher Scientific GmbH) using a PTFE sleeve. The emitters are a DESI- as well as an EASI- and a LTP-emitter. A thin spatula was used to apply small amounts of selected chemicals, pharmaceuticals and food products to microscope slides

or filter papers by slightly touching the surface. Operating parameters of the Orbitrap mass spectrometer were as follows: positive/negative ion mode for a scan range of 50 to 2000, spray voltage is set to 4.5 kV in case of DESI and disabled for EASI and LTP measurement, maximum injection time is 500 ms. Raw data files are analyzed using Xcalibur Qual Browser 4.1 software (Thermo Scientific).

[0050] Direct ambient mass spectrometric analyses are performed on both, a variety of chemicals and pharmaceutical drugs from a glass surface or filter paper as well as from the surface of real life samples. All mass spectra are recorded within a few seconds; the mass spectra of exemplary compounds are depicted in Figs. 6A - 6F, while Figs. 7A - 7B show the analysis of nutmegs and banana peels.

[0051] 4-Bromoacetophenone (Fig. 6A) and Cyclohexanone oxime (Fig. 6B) are directly measured from a glass surface using LTP as ionization source. In both cases, the protonated ($[M+H]^+$) species are detected at exceptional signal-to-noise ratios at m/z 198.975 respectively m/z 114.089.

[0052] Polypropylene glycol PPG1000 can be detected using DESI as well as EASI (Fig. 6D) and shows the expected normal distribution of chain lengths in the mass range from 700 to 1500, in which a single polyether was detected as the protonated ($[M+H]^+$), sodiated ($[M+Na]^+$) and potassiated ($[M+K]^+$) molecular ion. However, Benzoic acid (Fig. 6E) is particularly well detected in the negative ion-mode as a deprotonated ($[M-H]^-$) species using DESI/EASI at m/z 121.030.

[0053] The panels in Figs. 6C and 6F show the mass spectra obtained from standard samples of the organophosphate pesticide Chlorpyrifos detected using both LTP (Fig. 6C) as well as DESI/EASI (Fig. 6F). In case of LTP, the chemical appears as the protonated ($[M+H]^+$) molecule at m/z 349.933, while the potassiated ($[M+K]^+$) molecular ion at m/z 389.888 is detected using DESI and EASI.

[0054] Subsequently, it was checked whether the pen-like device can also be used for mass spectrometric analysis of biological samples, in particular food products. For this purpose, the surface of a nutmeg (Fig. 7A) is touched with the inventive DESI/EASI/LTP-Pen and the ingredient Elemicin is detected within seconds at m/z 209.119 as protonated ($[M+H]^+$) species using the LTP ion source. Furthermore, a surface analysis of a banana peel is carried out as shown in Fig. 7B. The pesticide Azoxystrobin is detected as protonated ($[M+H]^+$), sodiated ($[M+Na]^+$) and potassiated ($[M+K]^+$) species utilizing DESI as well as EASI in the positive ion-mode.

[0055] Fig. 8 shows the effect of minute amounts of ozone, which were in-situ generated in the course of ion-molecule reactions in the low-temperature plasma region near the sample surface. The C=C double bond of Limonene, a cyclic monoterpene from the oil of citrus fruit peels, is attacked by ozone. As a consequence of ozonolysis, the ring is cleaved and the cleavage products are

clearly visible in the obtained mass spectrum.

Claims

1. Hand-held ionization device for ambient mass spectrometry comprising

- an outer housing (4),
- an ion transfer tube (3),
- an ion source comprising

- a first emitter (1),
- a second emitter (2),

- and a separate control unit (6),

wherein parts of the ion transfer tube (3) and the ion source are inside the outer housing (4), wherein the first emitter (1) comprises a plasma device, preferably a low-temperature plasma (LTP) device, wherein the second emitter (2) comprises a sprayer device, preferably a desorption electrospray ionization (DESI) sprayer device as well as an easy ambient sonic-spray ionization (EASI) sprayer device, wherein the position of the parts of the ion transfer tube (3) and the ion sources (1, 2), which are inside the outer housing (4), is fixed, wherein the separate control unit (6) allows to switch between the ion sources.

2. Hand-held ionization device according to claim 1, wherein the outer housing (4) has the shape of a pen, wherein the tip of the pen is tapered and open.

3. Hand-held ionization device according to one of the claims 1 to 2 **characterized by** a camera module (5).

4. Hand-held ionization device according to claims 2 and 3, wherein the camera module (5) is mounted on the tapered tip of the pen outside the housing (4).

5. Hand-held ionization device according to one of the claims 1 to 4 **characterized by** an angle γ between an imaginary line perpendicular to the surface of interest and the hand-held ionization device, wherein the angle γ is between 25° and 45°.

6. Hand-held ionization device according to one of the claims 1 to 5, wherein the ion transfer tube (3) comprises a flexible tube (a) inside the outer housing (4), wherein the flexible tube (a) consists preferably of fluorinated ethylene propylene (FEP), polyethylene (PE), polyether ether ketone (PEEK) or any other kind of plastic tube.

7. Hand-held ionization device according to one of the claims 1 to 6, wherein the first emitter (1) comprising a LTP-emitter includes a glass capillary (b) which is

surrounded by an outer metal tape or metal wire electrode (c) in the vicinity of the tip of the outer housing (4), wherein a metal wire (d) is running through the inside of the glass capillary (b), wherein the inner diameter of the glass capillary is preferably between 0.4 and 1 mm and the outer diameter of the metal wire is preferably between 50 and 150 μm .

8. Hand-held ionization device according to one of the claims 1 to 7, wherein the second emitter (2) comprising a DESI-emitter as well as an EASI-emitter includes an inner capillary (j) flanged to a Y-shaped metal capillary (i), wherein the inner diameter of the inner capillary (j) is preferably between 40 and 60 μm and the inner diameter of the metal capillary (i) is preferably between 0.8 and 1.2 mm.

9. Hand-held ionization device according to one of the claims 7 or 8, wherein the parts of the ion transfer tube (3), the LTP-emitter (1) and the DESI/EASI-emitter (2) which are inside the outer housing (4) are arranged parallel along the longitudinal axis of the outer housing (4), wherein the distance between the ion transfer tube (3) and the LTP-emitter (1) is preferably between 3 and 7 mm, the distance between the LTP-emitter (1) and the DESI/EASI-emitter (2) is preferably between 1 and 4 mm and the distance between the ion transfer tube (3) and the DESI/EASI-emitter (2) is preferably between 4 and 10 mm.

10. Hand-held ionization device according to one of the claims 1 to 9, **characterized by** an additional tubing for suction-assisted extraction of aerosols from the cavity inside the tip of the device.

11. Mass spectrometry system comprising

an ion analysis instrument such as a mass spectrometer (7);
and a hand-held ionization device according to any of the preceding claims,

wherein the ion transfer channel (3) guides the ionized chemicals to the inlet of the ion analysis instrument (7).

12. Mass spectrometry system according to claim 11, wherein the ion analysis instrument (7) is connected to the hand-held ionization device via a PTFE sleeve, wherein this connection allows for an automatic change of settings in the ion analysis instrument (7) when the ion source in the hand-held ionization device is changed via the separate control unit (6).

13. Method for direct ambient mass spectrometry by using a mass spectrometry system according to the claims 11 or 12, wherein the hand-held ionization device can be moved freely over any sample surface,

wherein the ionization mode can be changed via the separate control unit (6), wherein the ionized molecules from the sample surface are analyzed in real time by the ion analysis instrument (7).

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14. Method for direct ambient mass spectrometry according to claim 13 by using a hand-held ionization device according to claim 3 and any of the claims 1 to 10, wherein the camera module (5) allows to optically track the device movement.

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15. Method for direct ambient mass spectrometry according to any of the claims 13 to 14, **characterized by** a consecutive use of the LTP-emitter and the DESI- or EASI-emitter, wherein the LTP-emitter is used for an in-situ modification of the sample surface, wherein DESI- or EASI-emitter is used for ionizing the molecules on the modified sample surface.

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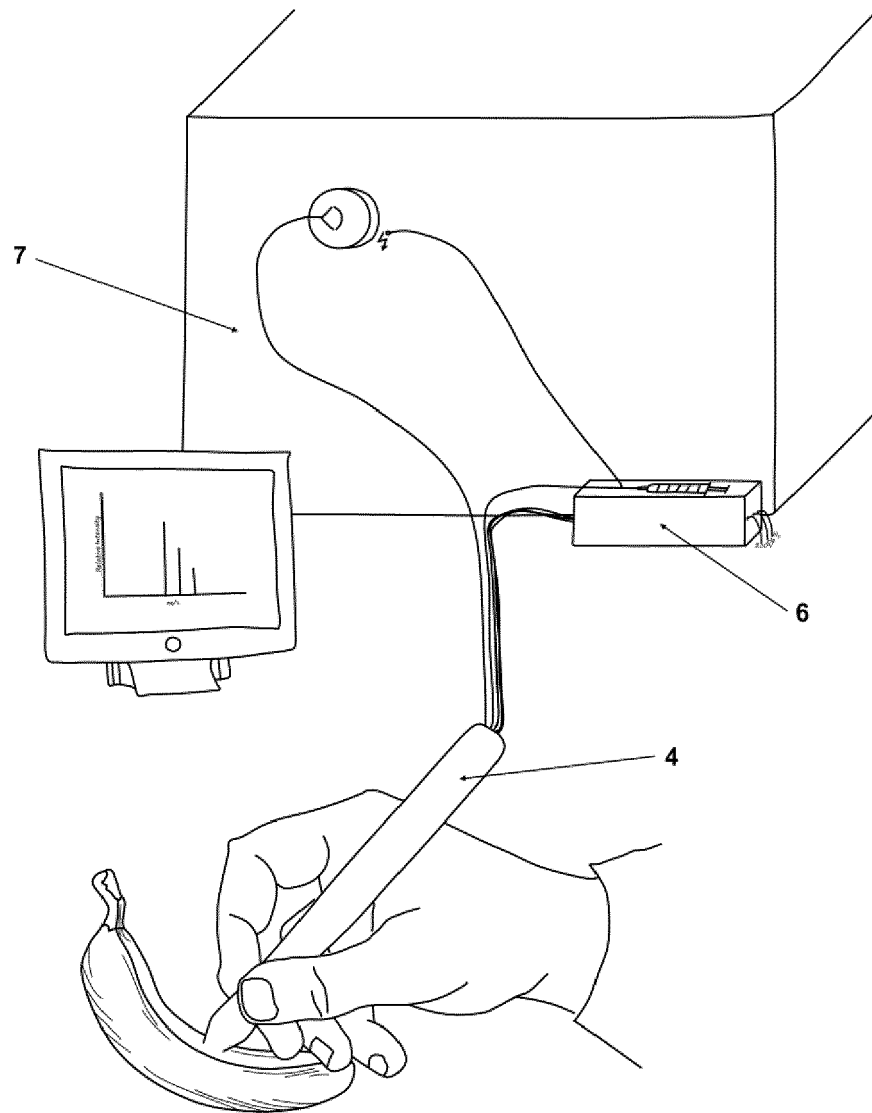


Fig. 1

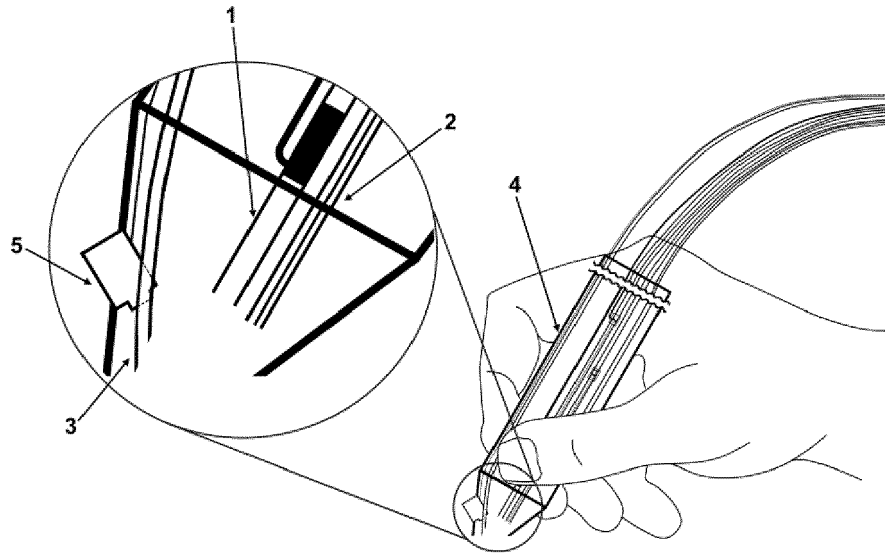


Fig. 2

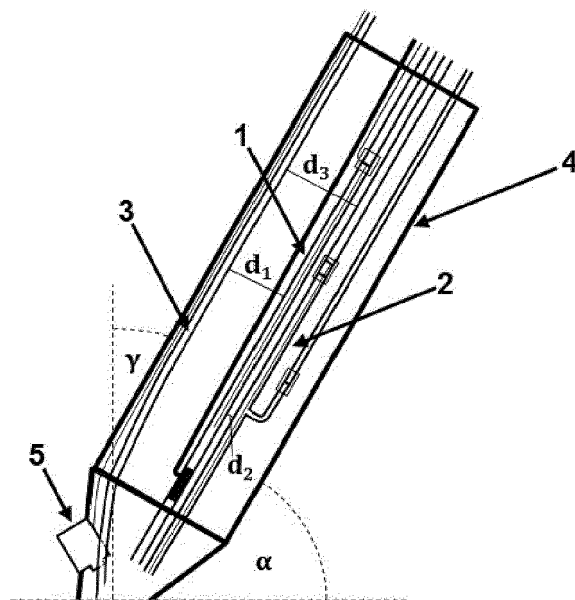


Fig. 3

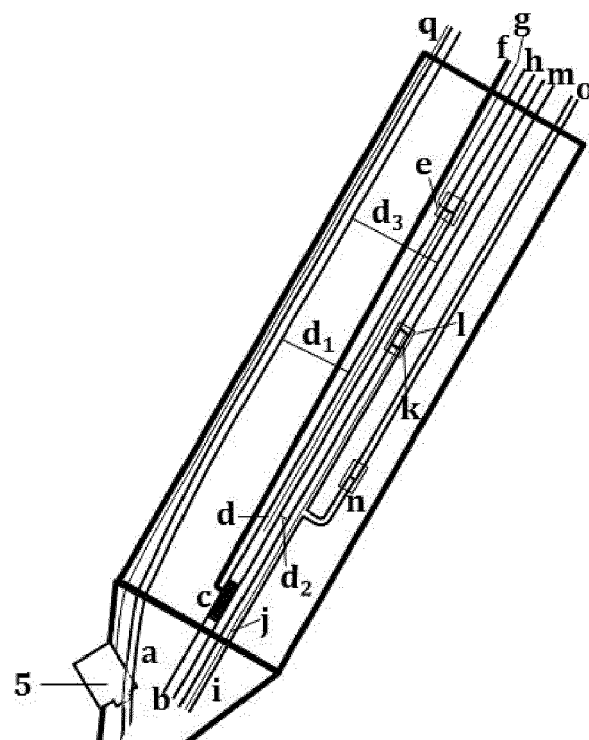


Fig. 4

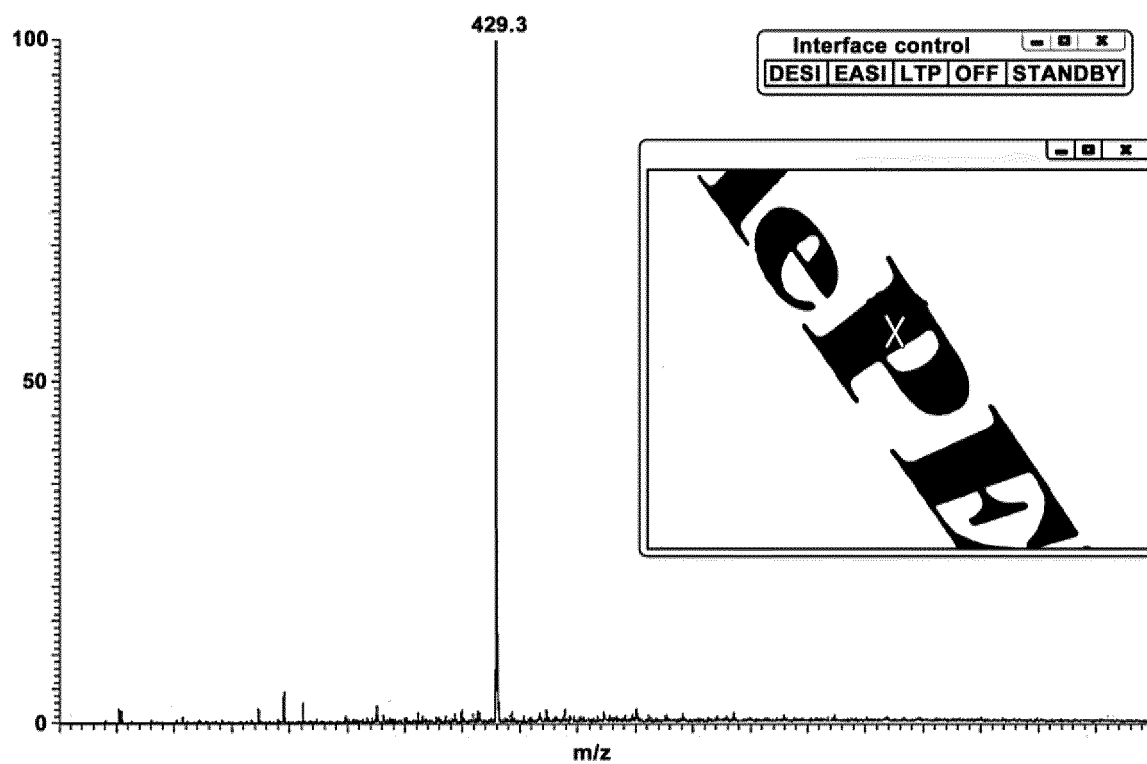


Fig. 5

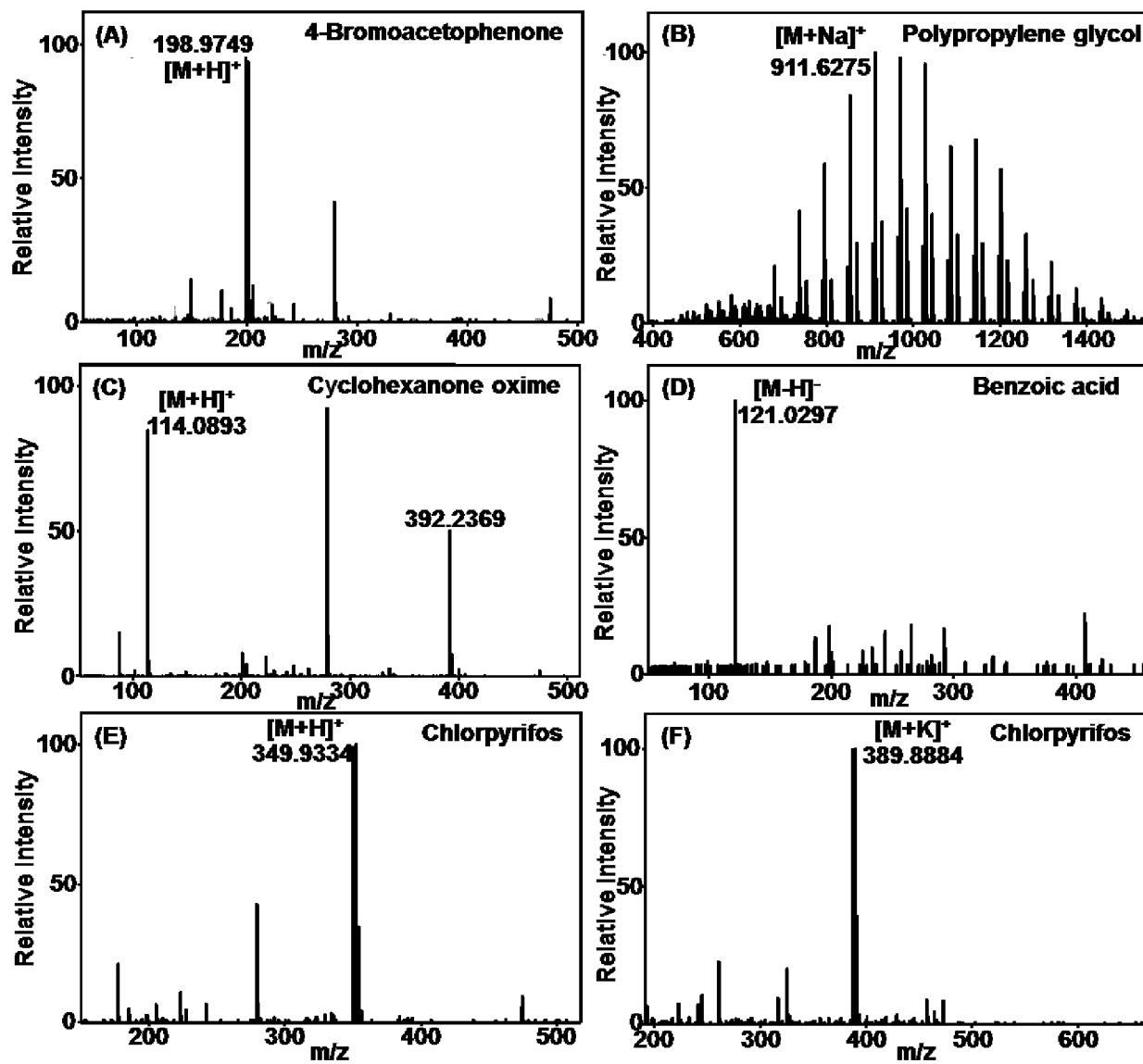


Fig. 6

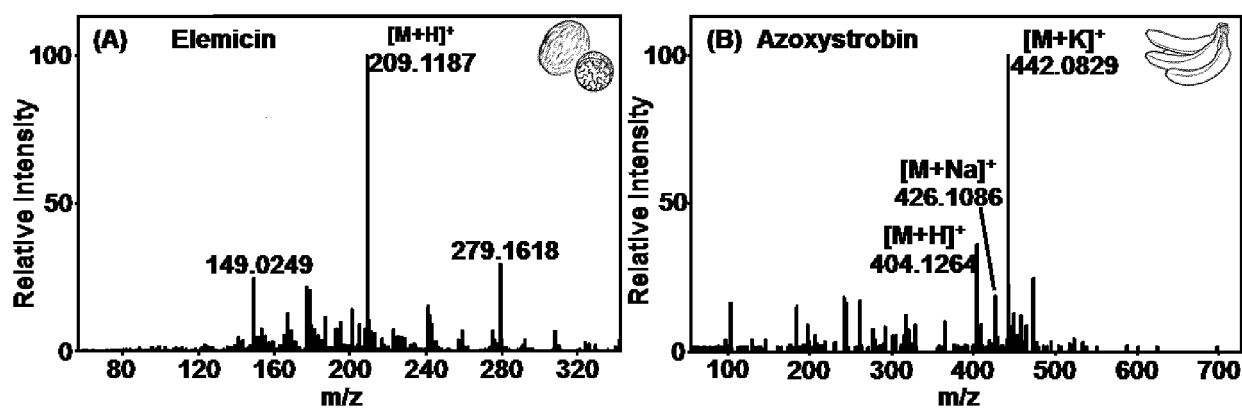


Fig. 7

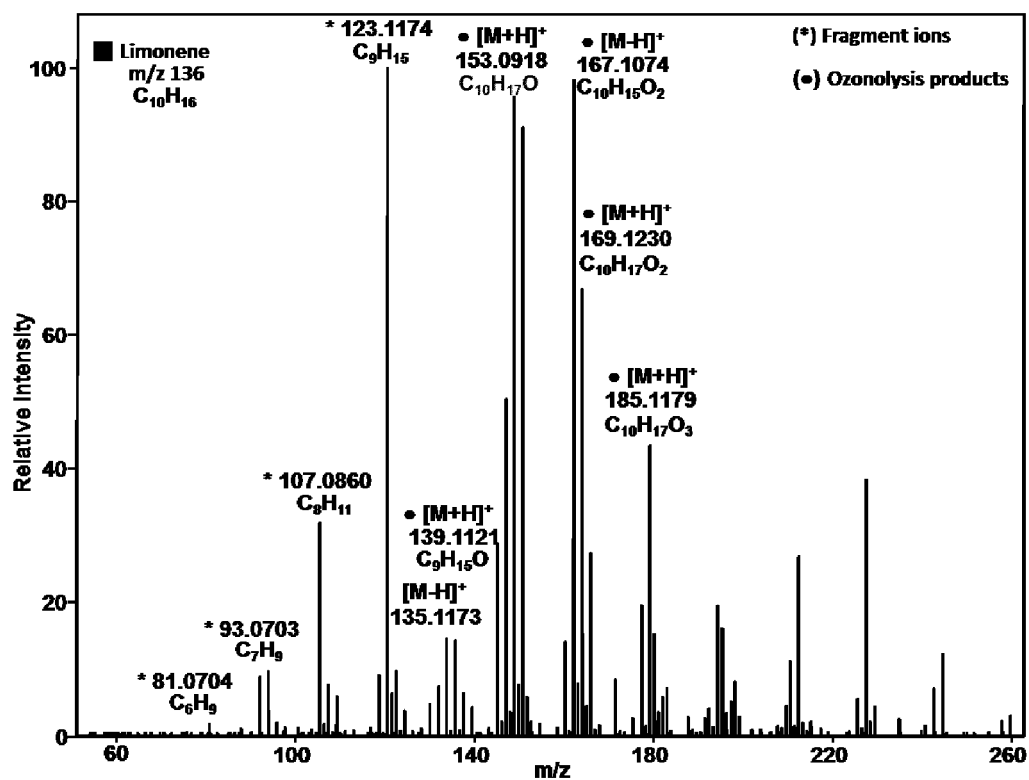


Fig. 8



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The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 12 November 2020	Examiner Loiseleur, Pierre
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Place of search The Hague		Date of completion of the search 12 November 2020	Examiner Loiseleur, Pierre
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