(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2012 (15.11.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/154859 A1

(51) International Patent Classification:
B05B 1/02 (2006.01)

(21) International Application Number:
PCT/US2012/037132

(22) International Filing Date:
9 May 2012 (09.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/484,048 9 May 2011 (09.05.2011) 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, 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, IS, JP, KE, KG, KM, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, ML, MR, NE, SN, TD, TG).

Published:

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

(54) **Title**: NOZZLES FOR NASAL DRUG DELIVERY

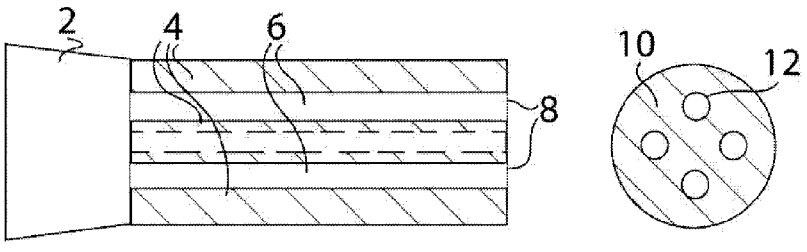


FIG. 1

(57) **Abstract**: A nozzle for use in delivering a mixture of aerosol propellant and drug formulation. The nozzle includes a drug product inlet configured to receive a mixture of aerosolized propellant and an intranasal dosage form. The inlet is disposed at the proximal end. A nozzle body is secured to the drug product inlet. Two or more channels are disposed within the body. Two or more orifice apertures are disposed at the distal end of the nozzle.

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NOZZLES FOR NASAL DRUG DELIVERY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Serial No. 61/484,048, filed May 9, 2011, the entire contents of which are hereby incorporated by reference herein in their entirety.

STATEMENT CONCERNING GOVERNMENT INTEREST

[0002] The instant invention was made with U.S. government funding pursuant to US Army SBIR grant W81XWH-10-C-0238. The Government may have certain rights in this application.

BACKGROUND

[0003] Existing nasal drug delivery devices do a poor job of penetrating the nasal cavity to deposit drug onto the medial turbinates for systemic delivery. Such existing devices are also lacking in delivering drug to the upper nasal cavity for direct nose-to-brain delivery. Existing nasal drug delivery devices generate a wide plume which inadequately delivers a compound deep into the nasal cavity.

SUMMARY

[0004] In one embodiment, a nozzle is described and claimed including a drug product inlet configured to receive a mixture of aerosolized propellant and an intranasal dosage form, the inlet disposed at the proximal end, a nozzle body defining two or more channels, the channels having a proximal and distal end, the body defining a longitudinal axis, and, an orifice disposed at the distal end of each channel.

[0005] In an aspect, the channels are disposed parallel to the longitudinal axis.

[0006] In another aspect, the channels are disposed at an angle with respect to the longitudinal axis.

[0007] In an aspect, the nozzle includes from five to seven channels.

[0008] In an aspect, the channels are circular and tubular in shape.

[0009] In an aspect, the channels are conical in shape.

[00010] In an aspect, four circular orifice apertures configured in a square orientation are disposed at the distal end of the nozzle.

[00011] In an aspect, five circular orifice configured in a pentagonal orientation are disposed at the distal end of the nozzle.

[00012] In an aspect, six circular orifice configured in a hexagonal configuration are disposed at the distal end of the nozzle.

[00013] In an aspect, six circular orifice configured in a centered pentagonal configuration are disposed at the distal end of the nozzle.

[00014] In an aspect, four circular orifice configured linearly are disposed at the distal end of the nozzle.

[00015] In an aspect, four rectangular orifice configured radially are disposed at the distal end of the nozzle.

[00016] In an aspect, five star-shaped orifice configured in a pentagonal configuration are disposed at the distal end of the nozzle.

[00017] In an aspect, the channels are plastic or metal tubes, the body is a plastic or metal tube, and, voids are disposed between the channels and body.

[00018] In another embodiment, a nozzle for delivering a compound to an upper olfactory region of a user is disclosed including a nozzle body having a central axis, a plurality of channels housed within the nozzle body, the channels having a proximal end and

a distal end, an inlet disposed at the proximal end of the channel, an outlet orifice disposed at the distal end of the channel, the outlet orifice arranged parallel to the central axis of the nozzle.

[00019] In an aspect, a line drawn thru a point on the outlet orifice is an equal distance to the central axis of the nozzle.

[00020] In an aspect, the outlet orifices are arranged so that a narrow plume exits the nozzle.

[00021] In an aspect, the angle of the plume is about 5 degrees, about 4 degrees, about 3 degrees, about 2 degrees, about 1 degree.

[00022] In yet another aspect, the angle of the plume is about 5 degrees.

[00023] In an aspect, the impact force delivered by the nozzle is decreased.

[00024] In an aspect, the delivery time for the compound is decreased.

[00025] In another embodiment, a nozzle for delivering a compound to an upper olfactory region of a user is disclosed including a nozzle body, a compound channel housed within the nozzle body, the compound channel having a proximal end and a distal end, the proximal end capable of receiving a compound, the distal end of the compound channel having an outlet orifice, and a propellant channel, the propellant channel having a proximal end and a distal end, the proximal end capable of receiving a propellant, the distal end of the propellant channel having an outlet orifice, the compound channel being centered within the propellant channel wherein the compound and the propellant are capable of being emitted from the from outlet orifice.

[00026] In an aspect, the nozzle includes at least a second compound channel, wherein the nozzle is capable of delivering more than one compound at a time.

[00027] In another aspect, the compound delivered by the nozzle is a liquid, a powder, a gas, or combinations thereof.

[00028] In another aspect, the nozzle further includes a check shut off valve wherein the check shut off valve prevents propellant from flowing through the compound chamber once the compound is released.

DESCRIPTION OF DRAWINGS

[00029] FIG. 1 shows cross-sectional side view and distal view of a nozzle embodiment.

[00030] FIG. 2 shows a cross-sectional side view of another nozzle embodiment.

[00031] FIG. 3 shows a cross-sectional side view of another nozzle embodiment.

[00032] FIG. 4 shows a cross-sectional side view of another nozzle embodiment.

[00033] FIG. 5 shows a cross-sectional side view of another nozzle embodiment.

[00034] FIG. 6 shows a cross-sectional distal view of another nozzle embodiment.

[00035] FIG. 7 shows a cross-sectional distal view of another nozzle embodiment.

[00036] FIG. 8 shows a cross-sectional distal view of another nozzle embodiment.

[00037] FIG. 9 shows a cross-sectional distal view of another nozzle embodiment.

[00038] FIG. 10 shows a cross-sectional distal view of another nozzle embodiment.

[00039] FIG. 11 shows a cross-sectional distal view of another nozzle embodiment.

[00040] FIG. 12 shows a cross-sectional distal view of another nozzle embodiment.

[00041] FIG. 13 shows a cross-sectional side view of another nozzle embodiment.

[00042] FIG. 14 shows a cross-sectional side view of another nozzle embodiment.

[00043] FIG. 15 is a graph of percent deposition versus vertical spray angle for various nozzle and outlet orifice embodiments set forth in the Examples and Figures herein. In this

graph the zero angle is defined as the optimal angle from the naris to the olfactory region.

[00044] FIG. 16 is a graph of percent deposition versus horizontal spray angle for various nozzle and outlet orifice embodiments set forth in the Examples and Figures herein. In this graph the zero angle is defined as the optimal angle from the naris to the olfactory region.

[00045] FIG. 17 is a photograph of the side and distal end of nozzle 18.

[00046] FIG. 18 is a photograph of the side and distal end of nozzle 35B.

[00047] FIG. 19 is a photograph of the side and distal end of nozzle 31.

[00048] FIG. 20 is a photograph of the side and distal end of nozzle 33.

[00049] FIG. 21 is a photograph of the side and distal end of nozzle 17.

[00050] FIG. 22 shows nozzle number 3.

[00051] FIG. 23 shows nozzle number 4.

[00052] FIG. 24 shows nozzle number 7.

[00053] FIG. 25 shows nozzle number 8.

[00054] FIG. 26 shows nozzle number 9.

[00055] FIG. 27 shows nozzles A, B, and C of Example 11.

[00056] FIG. 28 shows nozzle D of Example 11.

[00057] FIG. 29 shows a spray deposition (Method 3) comparison of 4 nozzles, two single channel nozzles and two 5 channel nozzles. Nozzle performance was tested over an extended distance range. To minimize the blotter wicking artifact, dose size was reduced to 10 microliters.

[00058] FIG. 30 shows frame captured images from high speed video of powder dosing. Comparison of plume geometry for three powder nozzles.

[00059] FIG. 31 shows frame capture from high speed video of powder plumes for a

zero bypass nozzle (simple tube) and a high bypass nozzle. These shots were carried out between two plastic plates with a spacing of 1.8mm, dimensions comparable to that found in the nasal sinus. Two times during the development of the plume after actuation initiation are shown. The performances with two different propellants are also compared.

DETAILED DESCRIPTION

[00060] Described herein are nozzles that deliver a compound into the posterior regions of the nasal cavity. Current nasal delivery systems do not adequately deposit drug in posterior regions of the nasal cavity such as the respiratory epithelium and olfactory region. Described herein are nozzles that enhance drug deposition into these regions of the nasal cavity.

[00061] The nozzles disclosed herein consistently deposit at least a majority fraction of dose into the distal parts of the nasal cavity such as the respiratory epithelium and olfactory region. A drug product (also referred to as drug formulation, nasal dosage form and other like terms used in the art) is propelled with a velocity via the nozzle into the nasal cavity.

[00062] The nozzle may be used to deliver a compound to the upper olfactory region of a mammal or other animal. For instance, the user may be a human or non-human primate. The nozzle may have adult or pediatric users. In some aspects, the nozzle may be used in veterinary medicine. In some aspects, the nozzle may be used to deliver a therapeutic or palliative care compound.

[00063] Like named structures in the various embodiments function in the similar or same manner, are structurally the same or similar, and may be used in for the same or similar purpose.

[00064] A nozzle is disclosed with a plurality of outlet orifices for delivery of a compound. The nozzle has a central longitudinal axis. The nozzle houses a plurality of

channels. The channels have a proximal end at which the compound to be delivered enters the channel and a distal end at which the compound exits the channel via an outlet orifice. In certain embodiments, the channels run parallel to the central axis of the nozzle. In other embodiments, the channels run substantially parallel to the central axis of the nozzle in that a line drawn thru a point on the outlet orifice is of equal distance to the central axis of the nozzle.

[00065] The outlet orifices are arranged in parallel alignment with the central axis of the nozzle. In one aspect, the outlet orifices are arranged where a line drawn through the orifice has an equal distance from a line drawn through the center of the nozzle. In yet another aspect, the arrangement of the outlet orifices of the nozzle provides a narrow plume. In yet a further aspect, the outlet orifices are arranged so that the initial path of the compound as it exits the nozzle is substantially parallel to the central axis of the nozzle. In yet another aspect, the outlet orifices are arranged in parallel alignment, in a line of equal distance from a center of the nozzle, in an arrangement that provides for the delivery of a narrow plume, in an arrangement that provides an initial path of the compound as it exits the nozzle substantially parallel to the central axis, or combinations thereof.

[00066] In an embodiment, the angle of the plume delivered from the nozzle is about 5 degrees, about 4 degrees, about 3 degrees, about 2 degrees, about 1 degree, inclusive of endpoints. In an embodiment, the angle of the plume delivered from the nozzle is about 5 degrees. In yet another embodiment, the angle of the plume is 5 degrees, is 4 degrees, is 3 degrees, is 2 degrees, or is 1 degree. In a further embodiment, the angle of the plume delivered from the nozzle is 5 degrees.

[00067] In embodiments of the nozzle, the impact force delivered by the nozzle having more than one outlet orifice is decreased.

[00068] In embodiments of the nozzle, the delivery time is decreased for delivery of a compound by a nozzle having more than one outlet orifice.

[00069] In another embodiment of the nozzle, the delivery time and the impact force is decreased by a nozzle having more than one outlet orifice.

[00070] In embodiments of the nozzle, the outlet orifices are arranged so that the propellant entrains the compound to be delivered. Without being bound by theory with regards to entrainment of the compound, the multiple streams exiting the nozzle created by the plurality of outlet orifices are better able to entrain air within the plume, thereby shielding the edges of the plume against friction induced turbulence at the edges of the plume.

[00071] As shown in FIG. 1, a drug product inlet 2 is configured to receive a mixture of gas propellant and a drug formulation. The drug formulation (prior to mixing with the gas propellant) may be in the form of a powder, dispersion, liquid or other suitable nasal delivery dosage form. A nozzle body 4 is secured to the drug product inlet 2. The mixture of gas propellant and drug formulation pass through circular, tube-shaped nozzle channels 6 before exiting the outlet orifices 8, 12 thus releasing the mixture. The circular, tube-shaped nozzle channels 6 aligned parallel to a longitudinal axis running through the center of the nozzle body 4. The distal surface 10 of the nozzle body 4 is shown in the distal view along with the outlet orifices 12.

[00072] In one embodiment, the drug product inlet may be optional. In another embodiment, the nozzle has an attachment mechanism to the source of the compound being distributed from the nozzle. The attachment mechanism may be a screw, snap or other suitable mechanism. In another embodiment, the drug product inlet and nozzle may be of uniform construction with the chamber, container or the like holding the compound being

delivered. When the drug product inlet is optional, a proximal end of the nozzle functions as the drug product inlet.

[00073] The channels may be circular, oval, square, triangular, parallelograms, trapezoidal or combinations thereof.

[00074] In one embodiment, the nozzle shown in FIG. 1 is described in Example 6.

[00075] As shown in FIG. 2, a drug product inlet 14 is configured to receive a mixture of gas propellant and a drug formulation. A nozzle body 16 is secured to the drug product inlet 14. The mixture of gas propellant and drug formulation pass through circular, tube-shaped nozzle channels 18 before exiting the outlet orifices 20 thus releasing the mixture. The circular, tube-shaped nozzle channels 18 being tapered away from a longitudinal axis running through the center of the nozzle body 16.

[00076] As shown in FIG. 3, a drug product inlet 22 is configured to receive a mixture of gas propellant and a drug formulation. A nozzle body 24 is secured to the drug product inlet 22. The mixture of gas propellant and drug formulation pass through circular, tube-shaped nozzle channels 26 before exiting the outlet orifices 28. The circular, tube-shaped nozzle channels 26 being tapered toward a longitudinal axis running through the center of the nozzle body 24.

[00077] As shown in FIG. 4, a drug product inlet 30 is configured to receive a mixture of gas propellant and drug formulation. A nozzle body 32 is secured to the drug product inlet 30. The mixture of gas propellant and drug formulation pass through conically-shaped channels 34 before exiting the outlet orifices 36 thus releasing the mixture. The conically-shaped channels 34 are aligned to taper away from a longitudinal axis running through the center of the nozzle body 32. The outlet orifices 36 (at the distal end of the channels 34) being larger in diameter than the proximal end of the channels 34.

[00078] As shown in FIG. 5, a drug product inlet 38 is configured to receive a mixture of gas propellant and drug formulation. A nozzle body 40 is secured to the drug product inlet 38. The mixture of gas propellant and drug formulation pass through conically-shaped channels 42 before exiting the outlet orifices 44 thus releasing the mixture. An axis along the center of the conically-shaped channels 42 being parallel to a longitudinal axis running through the center of the nozzle body 40. The outlet orifices 44 (at the distal end of the channels 42) being smaller in diameter than the channels 42 at the proximal end of the channels 42.

[00079] Shown in FIG. 6 are five (5) circular outlet orifices 48 disposed at the distal end of a nozzle body 46 in a pentagonal orientation. Shown in FIG. 7 are six (6) circular outlet orifices 52 disposed at the distal end of a nozzle body 50 in a hexagonal orientation. Shown in FIG. 8 are six (6) circular outlet orifices 56 disposed at the distal end of a nozzle body 54 in a centered-pentagonal orientation. Shown in FIG. 9 are four (4) circular outlet orifices 60 disposed at the distal end of a nozzle body 58 in a linear orientation. Shown in FIG. 10 are four (4) rectangular outlet orifices 64 disposed at the distal end of a nozzle body 62 in a radial orientation. Shown in FIG. 11 are five (5) star-shaped outlet orifices 68 disposed at the distal end of a nozzle body 66 in a pentagonal orientation. As shown in FIGS. 6-11, the volume between outlet orifices 48, 52, 56, 60, 64, 68 is solid. In another embodiment, the volumes may be void, partially void or partially solid.

[00080] In one embodiment, the outlet orifices are square, circular, oval, trapezoidal, parallelograms, triangular, star shaped, or combinations thereof.

[00081] In one embodiment, the nozzle shown in FIG. 6 is described in Example 1.

[00082] In another embodiment, the nozzle shown in FIG. 9 is described in Example 3.

[00083] Shown in FIG. 12 are five (5) circular outlet orifices 74 disposed at the distal end of the nozzle body 70 in a pentagonal orientation. In this embodiment, the volume 72 between the channels is void (e.g., an air gap).

[00084] In one embodiment, the nozzle shown in FIG. 12 is described in Example 2.

[00085] As shown in FIG. 13, a drug product inlet 76 is configured to receive a mixture of gas propellant and a drug formulation. A nozzle body 78 is secured to the drug product inlet 76. The mixture of gas propellant and drug formulation pass through circular, tube-shaped nozzle channels 80 before exiting the outlet orifices 82 thus releasing the mixture. In this embodiment the outlet orifices channels 80 extend beyond the nozzle body 78 and terminate at the outlet orifices 82 which are biased with the biased edge oriented near to and parallel to a longitudinal axis running through the center of the nozzle body 78. Nozzle #35B, as shown in FIG. 18, has outlet orifice channels which extend beyond the nozzle body.

[00086] In one embodiment, the nozzle shown in FIG. 13 is described in Example 4.

[00087] As shown in FIG. 14, a drug product inlet 84 is configured to receive a mixture of gas propellant and a drug formulation. A nozzle body 88 is secured to the drug product inlet 84. The mixture of gas propellant and drug formulation pass through circular, tube-shaped nozzle channels 90 before exiting the outlet orifices 92 thus releasing the mixture. In this embodiment there is a rounded inlet guide 86 attached to the nozzle body 88 and pointed into the drug product inlet 84 which directs the drug product into the nozzle channels 90. There also exists an outlet directional guide which guides the drug product coming out of the outlet orifices 92 to help maintain a narrow drug product spray. The nozzle is nozzle 31 shown in FIG. 19.

[00088] In one embodiment, the nozzle shown in FIG. 19 is described in Example 5.

[00089] As shown in FIGS. 27 and 28, a bypass nozzle is shown and described. Nozzle C (Example 11) describes an annular gas bypass nozzle. Nozzle C includes a chamber for the compound to be delivered and a chamber for the propellant. In one aspect, the compound is a drug and the propellant is a gas. The drug may be in liquid or powder form. Nozzle C includes a channel to transport the drug. This drug channel is centered inside of another channel, the propellant channel, which serves to deliver the propellant. In one aspect, the drug channel transports a powder while the propellant channel delivers a gas. The dimensions of the drug channel with respect to the propellant channel affects the amount and velocity of gas emitted from the outlet of the nozzle. Both the powder transport channel and the gas channel can be altered to change the performance of the nozzle assembly, as discussed in Example 11.

[00090] Upon actuation of nozzle C, both chambers are pressurized and gas is emitted from the end of the nozzle as a uniform and symmetrical hollow cylinder, while at the same time the dose is emitted into the center of the gas cylinder. Depending on the configuration of the two channels and the amount and type of gas used to drive the nozzle, the relative velocity of the gas and powder streams can be different, causing different effects on performance. In one embodiment, multiple dose transport channels are placed in the center of the gas transport tube so that this nozzle design would deliver doses of more than one drug at the same time with minimal mixing before the drugs are deposited on the target surface or tissue.

[00091] In one embodiment, the drug channel can transport a liquid, a powder, a gas, or combinations thereof.

[00092] In one embodiment, a bypass nozzle D is shown as in Figure 28. Nozzle D shows a check shut off valve. The valve includes a ball of plastic slightly smaller than the

diameter of the compound chamber behind the nozzle. Upon activation of the device, the ball rolls up behind the drug and seats on the back side of nozzle D, thereby effectively preventing gas flow through the drug channel once the drug is released.

[00093] A variety of compounds may be delivered by the nozzle. In one embodiment, a mixture of drug and gas propellant is delivered by the nozzle. In another embodiment, a mixture of liquid propellant and drug is delivered by the nozzle. In another embodiment, a liquid propellant is delivered by the nozzle. In yet another embodiment, a drug is delivered by the nozzle. In yet other embodiments, a combination of compounds is delivered by the nozzle.

[00094] The compound delivered by the nozzle may be a liquid, gas, solid, or combinations thereof. The compound may be a liquid or a powder. The compound may be a drug.

[00095] The nozzle may be used to deliver compounds to many environments. The nozzle may be used to deliver a compound intranasally. The nozzle may be used to deliver a compound orally, rectally, vaginally, topically, to the eye, or intranasally.

[00096] The nozzle may be used to deliver medicaments or other compounds not for therapeutic use. For example, the nozzle may be used to deliver a precise plume in manufacturing.

EXAMPLES

[00097] Set forth below are examples of nozzles and outlet orifices.

Example 1

[00098] In nozzle number 1, a five outlet nozzle was constructed of 30 gauge (G) stainless steel tubes, (approximately 0.0069 inch circular orifice and approximately 5mm in length) mounted within a 20G stainless steel tube. The 30G tubes fit tightly and formed a

symmetric pentagonal arrangement that would lie symmetrically on a circle. All non-orifice gaps between the individual 30G tubes were filled. The distal end of the nozzle was finished with all tubes flush and of equal length. The openings were finished clean and square.

Example 2

[00099] Nozzle number 2 was constructed having 11 outlets composed of 5, 25G stainless tubes (approximately 0.011 inch circular orifice and approximately 5mm in length) mounted within an 18G stainless steel tube for a tight fit. No voids between the 25G and 15G tubes were filled, so the nozzle configuration had 5 additional ports, approximately triangular in shape, the nozzle ports surrounding the 5 circular ports. In addition, a central void of roughly pentagonal shape exists at the very center which was capable of passing a dose. The distal end of the nozzle was finished with all tubes flush and of equal length. The openings were finished clean and square.

[000100] Nozzle number 3, as shown in FIG. 22, was constructed having 6 outlets composed of 3, 23G stainless tubes assembled into a 15G stainless steel tube. These fit tightly and no glue or filler was used. In addition to the three nozzle ports from the 23G tubes, there were three additional approximately triangular shaped outlets from the nozzle. The distal end of the nozzle was finished with all tubes flush and of equal length. The openings were finished clean and square.

[000101] Nozzle number 10 has some of the same components used to assemble nozzle number 3. For nozzle number 10, each 23G stainless tube has an approximately 30 degree bend in the last 2mm of the tube at the distal end of the nozzle. These tubes were inserted into a 14G stainless steel tube so that their orientation was all the same around the perimeter of the 14G tube. These were held in place with a central brass rod. The distal end of the nozzle was finished with all tubes flush and of equal length. The openings were finished

clean and square. Because of the 30 degree bend in the 23G tubes, they are oval in dimensions and not round. All voids between elements were open.

[000102] Nozzle number 11 has some of the same components of nozzle number 9 (Example 3) with straight 23G stainless steel tubes set into a 14G stainless steel tube. No brass rod was used to hold the tubes in, with the 14G tube being lightly crimped. The distal end of the nozzle was finished with all tubes flush and of equal length. The openings were finished clean and square. All voids between elements were open.

[000103] Nozzle number 13 has some of the same components as nozzle number 2. Similar to nozzle number 1 (Example 1), nozzle number 13 has all intervening open voids filled leaving 5 active nozzle ports in the same special relationship as those in nozzle number 2.

Example 3

[000104] Nozzle number 5 has four outlets of 30G stainless steel tubes in a linear arrangement within a modified 16G stainless steel tube. The 30G tubes were set by light crimping of the 16G tube and filler was applied to fill all voids between the 30G and 16G tubes. The distal end of the nozzle was finished with all tubes flush and of equal length. The openings were finished clean and square.

Example 4

[000105] Nozzle number 12 has five outlets consisting of 27G stainless steel needle ends arranged with the pointed ends extending beyond the end of the nozzle housing (a 16G stainless steel tube). All five 27G needles were arranged so that the point was placed closest to the center of the assembly. The assembly of 5 needles was secured within the 16G tube under tension from a centrally placed brass rod. The brass rod was tapered so that a tension fit held everything together. All voids other than the 5 outlet ports were filled with epoxy

prior to final assembly. The resulting nozzle had a tapered distal end that extended approximately 2.66mm from the end of the 16G nozzle housing. All port surfaces were finished clean and square.

[000106] Nozzle 19 is a composite assembly of nozzle number 37 (Example 6) with 27G stainless steel needles inserted into the port channels of a nozzle number 37 nozzle assembly. The needles extend from the plastic end of the distal end of the nozzle by approximately 5.5mm. The needles are all arranged so that the tip side of each needle is oriented toward the center of the nozzle. They lie closest to the central axis of the nozzle.

Example 5

[000107] Nozzle number 14 has seven outlet ports arranged around a central aerodynamic extension, analogous to nozzle number 7 (Example 8 and FIG. 24). Nozzle number 14 was cast in plastic rather than assembled with stainless steel tubing. The central extension is 2.15mm in diameter at the point that it joins the distal end of the nozzle and tapers in an aerodynamic fashion. The port channels are straight and parallel to the nozzle axis. The port channels are 5.5mm long. The nozzle assembly includes a female luer lock.

[000108] Nozzle number 15 is similar to nozzle number 14 but with the body of the section of the assembly before the nozzle proper being shorter while still including a female luer lock. Nozzle number 15 is cast entirely in plastic as a unit.

Example 6

[000109] Nozzle number 16 has 4 outlet ports arranged approximately 0.7mm apart and equidistant in a square pattern. Nozzle number 16 has a similar female luer lock design as for nozzle number 15 (Example 5). Port lumen lengths are approximately 5.3mm in length, parallel to each other and on axis with the nozzle body. Cast entirely in plastic as a unit.

[000110] Nozzle number 37 is similar to nozzle number 16, except 5 outlet ports arranged equidistant to each other and as if placed on a circle or the apices of a pentagon. Port channel lengths are 5.3mm and include the same luer lock as nozzle number 16. Cast entirely in plastic as a unit.

[000111] Nozzle number 38 has 4 outlet ports as in nozzle number 16. The port channels of nozzle number 38 traverse 10.3mm and they possess a right handed twist (as viewed at the distal end) of approximately 180 degrees in that distance. The nozzle is longer than nozzle 16 and contains the same luer features and spatial details as nozzle 16. Cast entirely in plastic as a unit.

Example 7

[000112] Nozzle number 4, as shown in FIG. 23, was constructed having 7 outlets composed of 3, 25G stainless tubes (approximately 21mm in length) assembled into a 15G stainless tube. The 15G tube was lightly crimped on its perimeter to secure the 25G tubes within the body. No adhesive was used and all voids remained open. The distal end of the nozzle was finished with all tubes flush and of equal length. The openings were finished clean and square.

Example 8

[000113] Nozzle number 7, as shown in FIG. 24, was constructed of 14, 30G stainless steel tubes arranged within a 14G stainless tube around a central steel aerodynamically sculpted pin. The 30G tubes are 14mm in length and are seated flush with the end of the 14G nozzle housing. The central pin is approximately 1.12mm in diameter. It protrudes from the distal end of the nozzle by 2.38mm. No glue is used to set these elements within the 14G tube. All perimeter voids participate in the movement of liquid and gas through the nozzle.

Except for the extended central pin, the distal end of the nozzle was finished with all tubes flush and of equal length. The openings were finished clean and square.

Example 9

[000114] Nozzle number 8, as shown in FIG. 25, has similarities to nozzle number 7 described in Example 8 without the use of 30G tubes on the periphery. Thin rectangular brass standoffs were used to center the central pin within the 14G stainless steel tube. Eight standoffs were required to center and maintain the pin in a linear orientation with respect to the 14G tube.

Example 10

[000115] Nozzle number 9, as shown in FIG. 26, is constructed of 14, 30G stainless steel needle tips with similarities to the 30G tubes of nozzle number 7. These tubes are mounted around the same type of central steel aerodynamically sculpted pin. Each tapered needle tip is mounted with the long side placed against the steel pin. The result is a 3mm tapered extension at the distal end beyond the edge of the 14G nozzle housing.

Example 11

[000116] Nozzles for the delivery of a dry powdered dose.

[000117] The nozzles of this Example are shown in FIG. 27 and 28.

[000118] Nozzle A. Single port nozzle. Several configurations of solid plastic drilled with a straight exit port of varying lengths were tested. A 4.45mm diameter plastic nozzle with a single 1.07mm internal diameter port of approximately 1cm in length was tested. Also tested was a 4.45mm in diameter nozzle with a single 0.67mm internal diameter port of 8.75mm in length. A third configuration was a nozzle of approximately 1cm in length with a

single nozzle port of 0.031inch internal diameter. The powder is driven through the port tube by gas pressure.

[000119] Nozzle B. Multiple port nozzle. Drilled in PEEK plastic. 5 nozzle ports of internal diameter of 0.015inch. Orifice diameters are 0.011 inches. The dose is driven through the multiple ports by gas pressure.

[000120] Nozzle C. Single port annular gas bypass nozzle. Two configurations were designed and tested. This nozzle design is a two compartment nozzle, one for the dose and one for gas. These nozzles feature a straight 0.031in internal diameter port tube that transports the powder. This transport tube is centered inside of another tube that serves to deliver a stream of gas. The configurations tested have different gas tube diameters and therefore affect the amount and velocity of gas emitted from the end of the nozzle. Both the powder transport tube and the gas tubes can be altered to change the performance of the nozzle assembly. These test configurations were designed to be driven by a single source of compressed gas (e.g. hydrofluoroalkane), but each compartment of the nozzle could be independently driven. Upon actuation, both chambers are pressurized and gas is emitted from the end of the nozzle as a uniform and symmetrical hollow cylinder, while at the same time the dose is emitted into the center of the gas cylinder. Depending on the configuration of the two tubes and the amount and type of gas used to drive the nozzle, the relative velocity of the gas and powder streams can be different, causing different effects on performance.

[000121] The inner diameter of the dose tube is 0.031in for all three nozzles. The zero (0) bypass nozzle is the third configuration described in A above. Low bypass nozzle has a gas tube gap of 0.008in. The high bypass nozzle has a gas tube gap of 0.016in.

[000122] Nozzle D. A variant of nozzle C was made and tested, shown in FIG. 28. It is possible that excess propellant gas emitted from the dose tube after the dose chamber is

emptied of powder can cause interference with the plume. In that event, a check shutoff valve was conceived and tested. The valve consisted of a ball of plastic slightly smaller than the diameter of the dose chamber behind the nozzle. Upon activation of the device, the ball rolls up behind the dose and then seats on the back side of the nozzle, thereby effectively preventing gas flow through the dose tube once the dose is gone.

Example 12

[000123] Analytical methods employed for nozzle testing

[000124] Plume geometry

[000125] Plume angle was tested as a performance criterion. The testing of the nozzles included establishing the angle of the plume and/or the size of the deposition area at a fixed distance from the nozzle tip.

[000126] 1) Photography. The pattern of expelled high pressure water from the nozzle was photographed and the angle described by the pattern on the printed photo was measured. This method proved to be accurate and reproducible. Additional methods would look at describing the plume angle of an aerosolized plume as would be generated during actual use. Photography data was used as comparison data for the nozzles described herein.

[000127] 2) Blotter paper deposition. A method was developed that relied on the deposition of a stained (Fluorescein) aqueous dose emitted from a nozzle onto a blotter paper held at a distance of 4cm. 4cm was chosen as a distance relevant to the distance needed to traverse from a likely nozzle tip position in the human naris to the upper olfactory region of the human nasal sinus. This blotter paper deposition assay offered the advantage of creating a permanent record of the dose deposition. In addition, it would be capable of showing any asymmetry in plume geometry. Plume angles were calculated using the blotter paper deposition. A limitation of this method is that the dose staining can bleed beyond the region

of deposition, thereby making the observed deposition spot to be larger than the actual deposition zone. This is especially true for larger dose volumes and for nozzles that concentrate the dose into the smallest zone. Another limitation is that the method describes the end result of the deposition and cannot describe how deposition occurs over the course of the event. This limitation yields less information about the nature of the plume as it starts, progresses and ends. It can say very little about how the plume is affected by its travels through the air from nozzle to target.

[000128] Two additional approaches designed to analyze plume geometry during the time course of dose delivery were applied.

[000129] 3) High speed blotter recording, with dose deposition onto a rapidly spinning blotter paper target. This method is able to create a physical record of deposition over time. The blotter disk can be rotated fast enough so that dose spread is reduced and appears to yield accurate plume geometries displayed during the full shot. It appears to be able to discriminate between different nozzle designs and can catch asymmetries in plume geometry.

[000130] 4) The second method is high speed videography (greater than 200 frames per second) enhanced with fluorescent dye and lighting. This method appears capable of discriminating the performance between different nozzle designs and can record defects in performance. This method has been adapted for studying nozzle performance under various situations, such as free air performance and within human nasal models.

[000131] 5) An adaptation of method high speed videography. Modified lighting conditions were used to enhance the visualization of powder doses. In some cases lighting was adjusted so that only limited sections of the spray plume were visible. White light illumination is valuable for seeing the overall plume geometry for powder, however white light is easily scattered and is not able to report on the various dose densities within a plume

and likely best highlights the surface of a powder plume. Using single wavelength light in the red spectrum is able to reduce light scatter and better penetrate a powder plume.

[000132] Dose Deposition

[000133] Previous methods are principally directed at understanding plume geometry generated by each nozzle. We used these methods to attain certain pre-determined performance parameters, such as symmetrical and narrow plumes, to predict actual performance in use. An *in vitro* method for assessing nozzle performance was to measure dose deposition efficiency in human nasal models. We have employed several methods for this, differing mostly in the manner in which we quantitate the amount of dose deposited in different areas of the human nasal sinus. Of the three methods developed, here we report data generated from two methods.

[000134] 5) One method assessed deposition by dose weight and was able to report only dose weight deposited in our upper olfactory region of interest (ROI) and elsewhere.

[000135] 6) Another method reports dose deposition through optical densitometry. This method is capable of reporting fractional deposition within our upper olfactory ROI as well as any number of other ROI that are user defined.

[000136] Impact Force

[000137] Another physical performance characteristic that affected nozzle design was the impact force generated by the developed plume from any nozzle. We developed a method that records impact force profiles (including maximal impact force) for the duration of a dose shot. Forces generated during dosing could be compared to other commercially available nasal spray devices.

[000138] Results:

[000139] Plume Geometry:

[000140] Many of the nozzles described herein have principle deposition zone dimensions of 3mm or less when fired 4cm from the target with relatively minor amounts of dose outside of 5mm. This represents a plume angle of about 5 degrees or under. It should be noted that the dimensions of the upper olfactory region of the human nasal sinus is on the order of several mm eventually narrowing down to 1-2mm.

[000141] An early deposition study (method 5) along with a study with method 3 allowed a direct comparison between some of the nozzles described in this application with a nozzle designed to generate a rotating plume and also to a single port device (urethral tip).

Table 1

Nozzle Name	Deposition Zone Dimensions - Method #3	% Olfactory Deposition - Method 5				
		Direct aim	10 degrees posterior	10 degrees anterior	5 degrees toward septum	5 degrees away from septum
Rotational Plume Prototype	25 -30mm	2.8	4.2	9.9	1.23	2.4
# 18	25mm	19	12.5	20.9	22	16
#2	13mm	58.3	30.2	49.1	45.6	54.8
#13	8mm	59.4	45.7	55.9	63.2	57.3
#1	*	66	66	67.4	64.3	65
Urethral Tip	**	56.5	28.7	39.5	35.8	52.3

* Not done concurrently with the other nozzles under the same conditions, however, later comparisons between #1 and #13 reveal that #1 has a smaller deposit footprint than #13.
** Not done

[000142] As shown in Table 1, high speed blotter paper deposition analysis was carried out with each nozzle in this experiment with the exceptions of nozzle number 1 and the urethral tip. Later comparisons with nozzle number 1 revealed that nozzle number 1 is able to achieve the smallest deposition zone for any of the nozzles tested. The urethral tip is also able to achieve a deposition zone approaching that of nozzle number 13.

[000143] The deposition study presented in Table 1 shows the average from at least three nozzle firings for each nozzle and each aim angle. All conditions of firing were the same for all the nozzles and for each firing condition studied. A correlation can be made between the size of the dose deposition zone and the percent of dose deposited in the upper olfactory region of a human nasal model. The correlation persists regardless of the aim angle used for these shots. We conclude that the smaller the dose plume angle is, the higher the deposition in our ROI. Not expected from these results is that some of the nozzles appear to perform better regardless of the aim of the nozzle. In contrast, the urethral tip, which has a single nozzle port and generates a single plum stream, appears to be more sensitive to aim angle. While the urethral tip has good deposition (though by no means the best) when aimed directly at the target, its performance falls off dramatically at most other angles. We generally see with this data that multiport nozzles, which generate multiple stream plumes, perform better in off-angles compared to the single port nozzle.

[000144] The experimental results presented in the FIG. 29 demonstrate how parallel multistream plumes appear to be more resistant to plume degradation over greater distances. All nozzles can be seen to have narrow deposition zones. The single port nozzles #20 and #21 appear to degrade faster upon distance from the nozzle tip. This can especially be seen with nozzle #21. The smallest diameter single port nozzle has comparability to the multi-dose nozzles, but the constraint of this narrow port (1/5th the port area of the 0.0069in 5 port nozzle) adversely affects the time of full dose delivery and/or the forces generated by the plume on potentially sensitive nasal membranes (see Table 2 below).

[000145] Two measured parameters, nasal model deposition and plume stability, point to a parallel multistream nozzle configuration being better able to maintain a narrow dose plume while traveling to the target. Our results demonstrate a narrow plume can deposit on

the narrow recessed upper olfactory region of the human nasal sinus. Also, a multistream dose plume appears to better negotiate the intricacies of the complex human sinus. The off-angle performance advantage for a multistream dose plume compared to the urethral catheter (e.g., a single port 0.020inch nozzle) demonstrates that clearly. Without being bound by theory, it may be that the ability of a multistream dose plume's ability to entrain air (essentially forming an air capsule) is capable of solving both of these challenges (nasal model deposition and plume stability). Such an air capsule may reduce peripheral turbulent degradation of the dose steam as well as buffer its interaction with the walls of the nasal sinus.

[000146] Table 2 addresses the property of shot duration for various narrow plume nozzles. Multi port nozzles have the advantage of initiating and completing dose delivery in relatively short times. In contrast, the best performing single port nozzle (with respect to deposition zone) required in excess of 50 milliseconds to complete a reduced volume dose. The single port nozzles would greatly limit the size of the dose that a device could deliver. A 50μL dose would take in excess of 100 milliseconds and a 100μL dose nearly 2/10ths of a second. This is too long for a user actuated device. Even if increasing the single port aperture to 0.020in, which could in theory bring the shot duration performance into line with the multiport nozzles, performance is lost, as shown in Tables 1 & FIG. 29. Alternatively, increased pressure might be able to reduce the shot time for nozzle #20, but the impact force from such a stream is more likely to be damaging to sensitive tissues.

Table 2

Spray Deposition - Method 3 - High Speed Disk					
Nozzle Name	Nozzle Description - Number of Ports & Port Diameter (inch)	Spray Deposition zone width @ 4cm	Fine Mist* Width @ 4cm	Spray dose volume** in µL	Spray duration Milliseconds
#1	5 ports @ 0.0069	1.95mm	10.26mm	30	28.4
#13	5 ports @ 0.0110	2.39mm	8.19mm	40	4.6
#22	5 ports @ 0.0060	2.18mm	9.73mm	40	19.1
#23	5 ports @ 0.0110	2.87mm	11.15mm	40	3.1
#20	1 port @ 0.0070	1.36mm	9.09	25	56.0

* Each spray deposition results in some small fraction of the dose that is deposited at some distance from the central dense deposition zone. This is measurable with this method and is likely less than 10% of the dose.
** The maximal dose load was 40µL for this experiment. However, for those nozzles with restricted flow, less volume was required in order to measure the greatly extended duration of the spray.

[000147] Table 2 shows physical dimensions of spray plume and duration of spray for 4 parallel multiport nozzles and one single port nozzle.

Example 13

[000148] Powder Nozzles

[000149] FIG. 30 shows the effect that a bypass nozzle can make on a plume of powder as it is ejected out of a nozzle into free air. In most cases a simple tubular powder nozzle will display what is shown in FIG. 30. The front of the plume appears to form a bullet point shape. Video analysis shows that likely mechanism causing this is that the powder is ejected from the nozzle as a ballistic stream and the leading edge is immediately met by resistance from the air that it is moving into. This appears to be met by additional material fed into the back of this turbulent feature. In cases where the nozzle has clogged mid shot, the "bullet" plume essentially comes to a rest. The propagation of the plume through the ambient air requires additional force from the fresh material emanating from the nozzle.

[000150] In contrast, the bypass nozzles do not possess this feature. The powder appears to be buffered against impact with any stationary air in the firing path. Without being bound by theory, we believe that the propellant that exits the nozzle has displaced the stationary air, replacing it with a forward moving stream of gas. This forward stream of gas likely paves the way or carries the powder as if on a slipstream moving in the direction aimed. Additional studies have shown what appears to be more tightly collimated powder streams when fired from the bypass nozzles, as shown in FIG. 30.

[000151] FIG. 31 demonstrates again how the high bypass generated slipstream appears to negate the leading edge bullet point and turbulence that a simple zero bypass nozzle generates. In this case where the plumes are directed between two plates 1.8mm apart also shows how the powder streams generated by the high bypass nozzle can remain collimated as compared to that caused by the zero bypass nozzles.

Example 14

[000152] Nozzle 18 was constructed of qty. five (5) metal tubes with an internal diameter of 0.01 inches and an external diameter of 0.02 inches contained within a 15 metal tube with an internal diameter of 0.054 inches and an external diameter of 0.070 inches. The metal tubes are frictionally secured. Air gaps are disposed between the needles. Nozzle 18 is illustrated in FIGS. 12 and 17.

[000153] Nozzle 35b included five (5) outlet orifices with a diameter of 0.008 inches which extend out from the housing body and terminate as sharp points. Nozzle 35b is illustrated in FIGS. 7, 13, and 18.

[000154] Nozzle 31 included qty. seven (7) outlet orifices with diameter of 0.015 inches. Nozzle 31 is illustrated in FIGS. 14 and 19.

[000155] Nozzle 33 included qty. five (5) outlet orifices each with a diameter of 0.015 inches. The outlet orifices on the distal end of Nozzle 33 are illustrated in FIGS. 6 and 20.

[000156] Nozzle 17 was constructed with five outlet orifices with a diameter of 0.006 inches. The outlet orifices on the distal end of Nozzle 17 are illustrated in FIGS. 6 and 21.

[000157] Set forth in Table 3 is data generated using various nozzles in accordance with the invention.

Table 3

Nozzle	Average deposition % @ 0 deg horizontal and vertical	Outlet Orifice Diameter (in)	Average Impact Force (grams)
29	62%	0.054	4.00 ± 0.22
18	58.3	0.054	4.06 ± 0.86
35B	45.7%	0.0075	2.04 ± 0.59
31	33.9%	0.015	2.42 ± 0.37
33	41.6%	0.015	2.32 ± 0.57
17	66.0%	0.007	1.99 ± 0.08

[000158] Average deposition was done with the nozzle aimed at optimal orientation into a human nasal sinus model. Depositions were determined by dose weights deposited onto model surfaces with the average of a minimum of three experiments.

[000159] Spray plume diameter and Average impact force measurements were taken with nozzles positioned at 4cm distant from recording device. Outlet orifice diameter is by direct measurement.

CLAIMS

We Claim:

1. A nozzle comprising:

a drug product inlet configured to receive a mixture of an aerosolized propellant and an intranasal dosage form, the drug product inlet disposed at a proximal end,

a nozzle body defining at least two channels, the channels having a proximal end and a distal end, the body defining a longitudinal axis, and,

an outlet orifice disposed at the distal end of each channel.

2. The nozzle of claim 1, wherein the channels are disposed parallel to the longitudinal axis.

3. The nozzle of claim 1, wherein the channels are disposed at an angle with respect to the longitudinal axis.

4. The nozzle of claim 1 further comprising at least five channels.

5. The nozzle of claim 1, wherein the channels are circular or tubular in shape.

6. The nozzle of claim 1, wherein the channels are conical in shape.

7. The nozzle of claim 1, further comprising four outlet orifices, wherein the outlet orifices are circular and arranged in a square.

8. The nozzle of claim 1, further comprising five outlet orifices, wherein the outlet orifices are circular in shape and arranged in a pentagon.

9. The nozzle of claim 1, further comprising six outlet orifices, wherein the outlet orifices are circular in shape and arranged in a hexagon.

10. The nozzle of claim 1, further comprising six outlet orifices, wherein five of the outlet orifices are configured in a pentagon and one outlet orifice is configured at the center of the pentagon.

11. The nozzle of claim 1, further comprising four outlet orifices, the outlet orifices arranged in a line.

12. The nozzle of claim 1, further comprising four outlet orifices, wherein the outlet orifices are rectangular in shape and radiate out from the center axis of the nozzle.

13. The nozzle of claim 1, further comprising five outlet orifices, wherein the outlet orifices are star shaped and arranged in a pentagon.

14. The nozzle of claim 1, wherein the channels are a plastic or a metal, the body is a plastic or a metal, and, a void is disposed between the channels and the body.

15. A nozzle for delivering a compound to an upper olfactory region of a user comprising:

a nozzle body having a central axis,

a plurality of channels housed within the nozzle body, the channel having a proximal and a distal end,

an inlet disposed at the proximal end of the channel,

an outlet orifice disposed at the distal end of the channel, the outlet orifice arranged parallel to the central axis of the nozzle.

16. The nozzle of claim 15, wherein a line drawn thru a point on the outlet orifice is an equal distance to the central axis of the nozzle.

17. The nozzle of claim 15, wherein the outlet orifices are arranged so that a narrow plume exits the nozzle.

18. The nozzle of claim 17, wherein the angle of the plume is about 5 degrees, about 4 degrees, about 3 degrees, about 2 degrees, about 1 degree.

19. The nozzle of claim 18, wherein the angle of the plume is 5 degrees.

20. The nozzle of claim 15, wherein an impact force delivered by the nozzle is decreased.

21. The nozzle of claim 15, wherein a delivery time for the compound is decreased.

22. A nozzle for delivering a compound to an upper olfactory region of a user comprising:

a nozzle body,

a compound channel housed within the nozzle body, the compound channel having a proximal end and a distal end, the proximal end capable of receiving a compound, the distal end of the compound channel having an outlet orifice, and

a propellant channel, the propellant channel having a proximal end and a distal end, the proximal end capable of receiving a propellant, the distal end of the propellant channel having an outlet orifice, the compound channel being centered within the propellant channel

wherein the compound and the propellant are capable of being emitted from the from the respective outlet orifice.

23. The nozzle of claim 22, further comprising at least a second compound channel, wherein the nozzle is capable of delivering more than one compound at a time.

24. The nozzle of claim 22, wherein the compound is a liquid, a powder, a gas, or combinations thereof.

25. The nozzle of claim 22, further comprising a check shut off valve wherein the check shut off valve prevents propellant from flowing through the compound chamber once the compound is released.

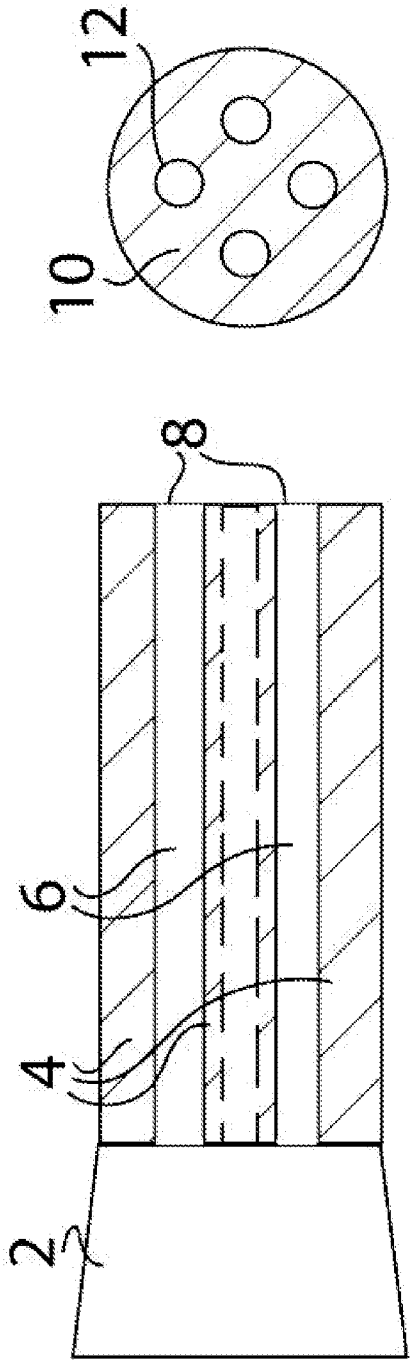


FIG. 1

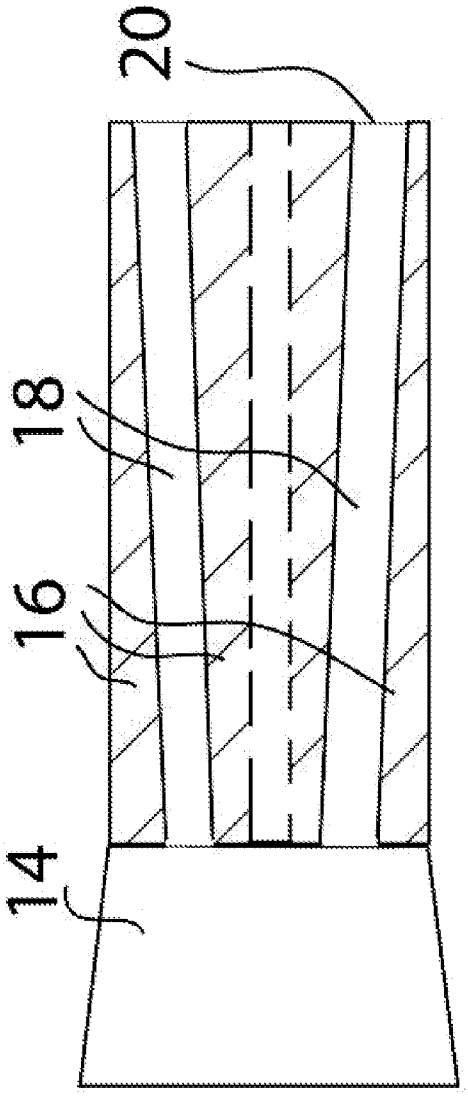


FIG. 2

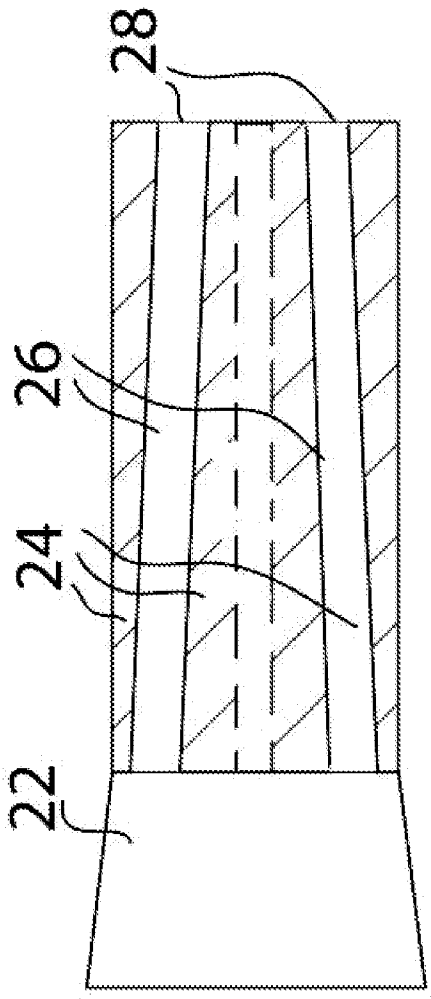


FIG. 3

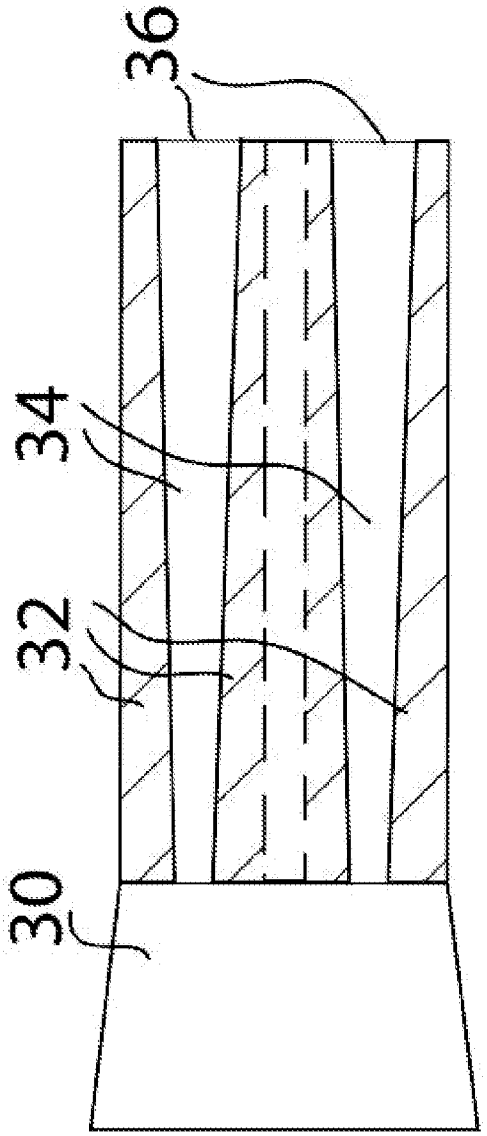


FIG. 4

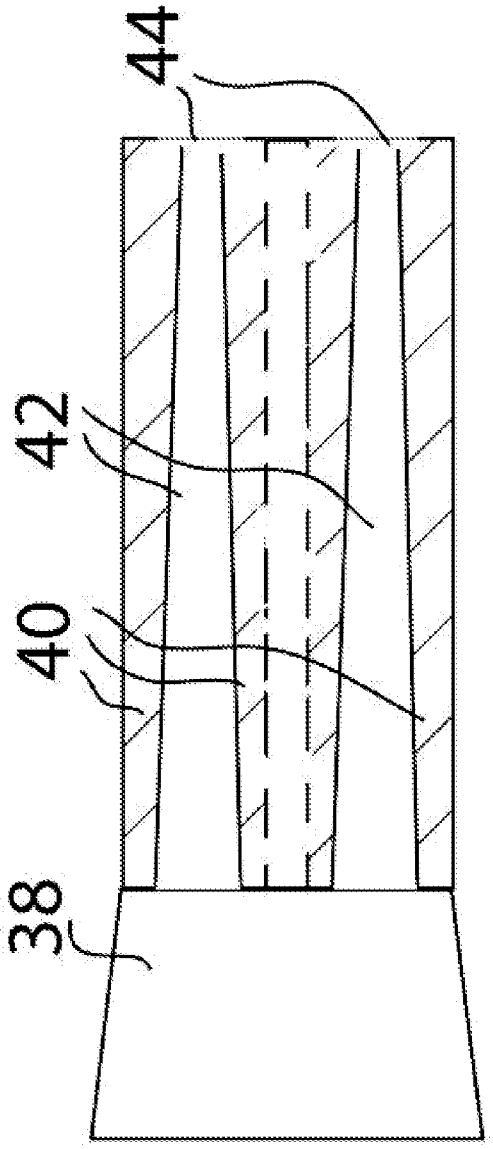


FIG. 5

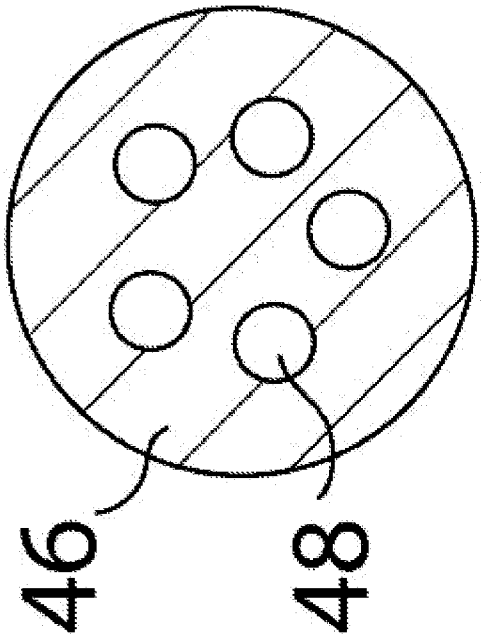


FIG. 6

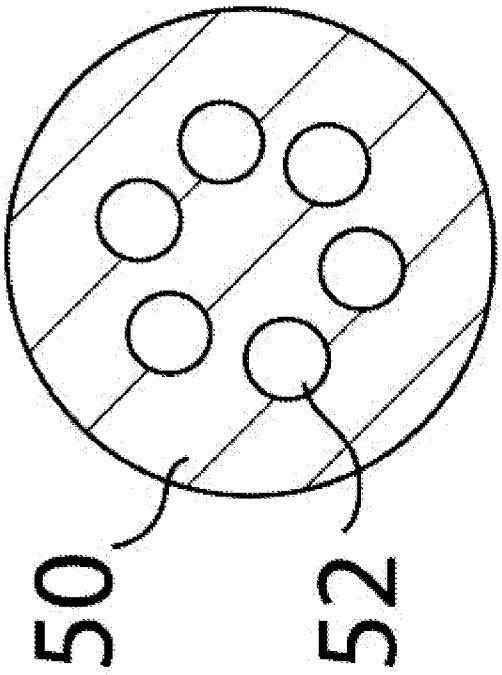


FIG. 7

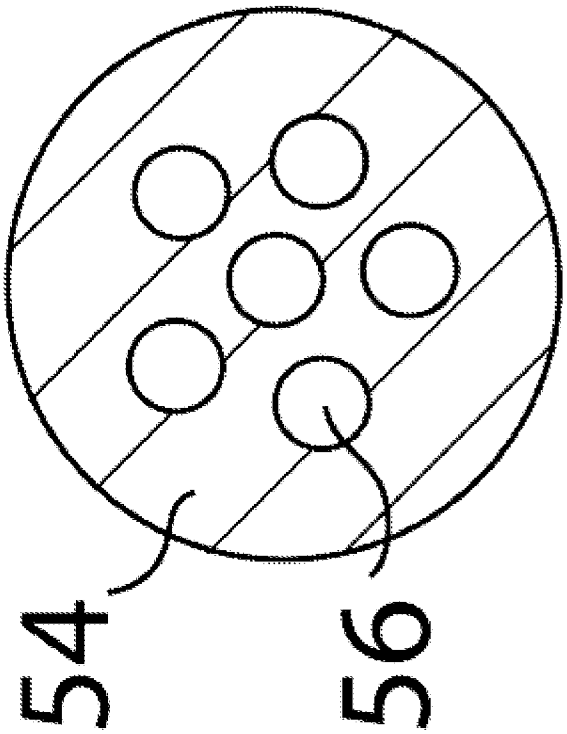


FIG. 8

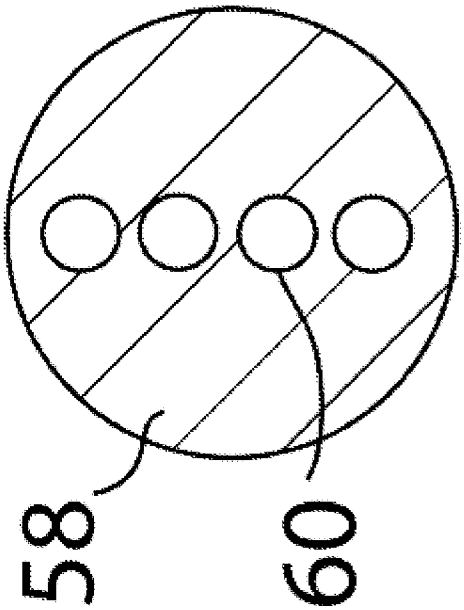


FIG. 9

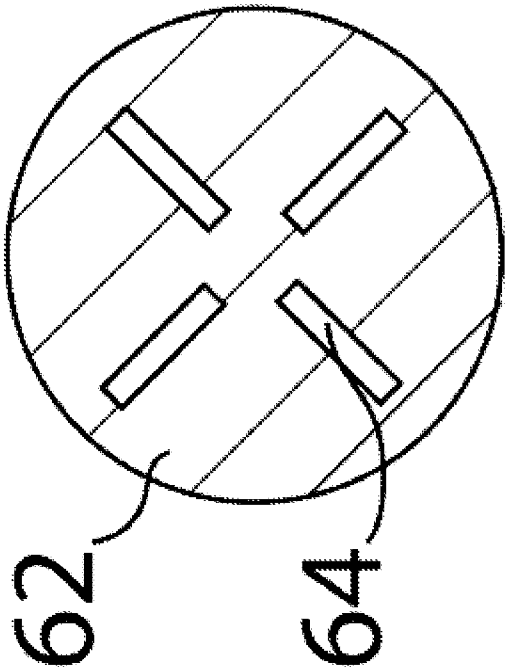


FIG. 10

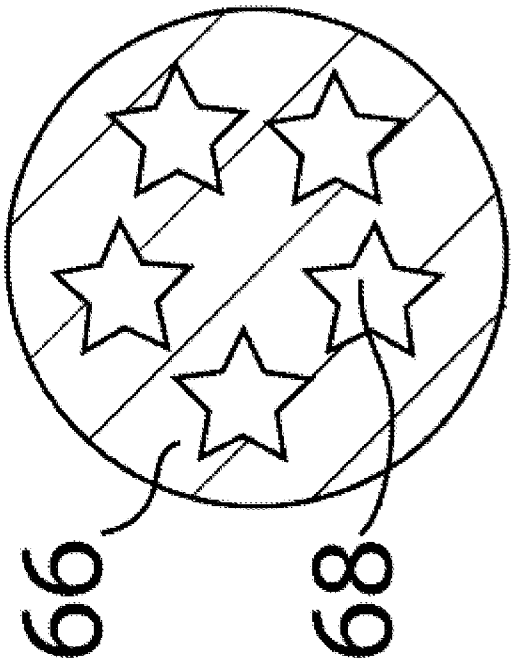


FIG. 11

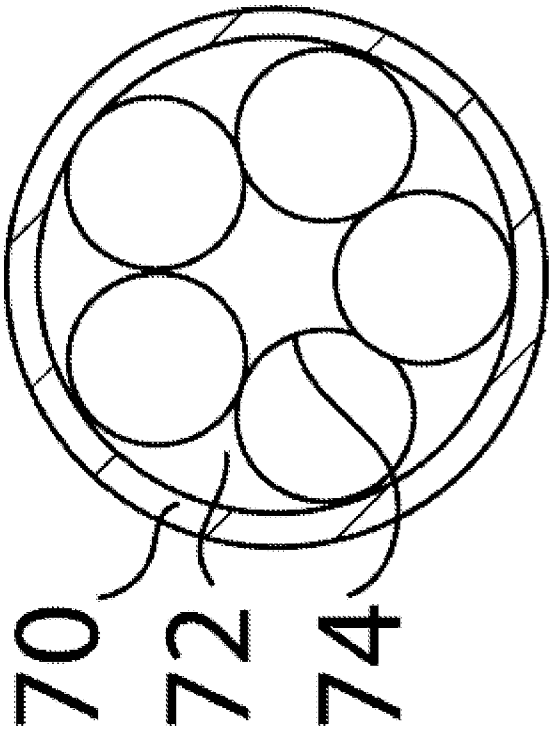


FIG. 12

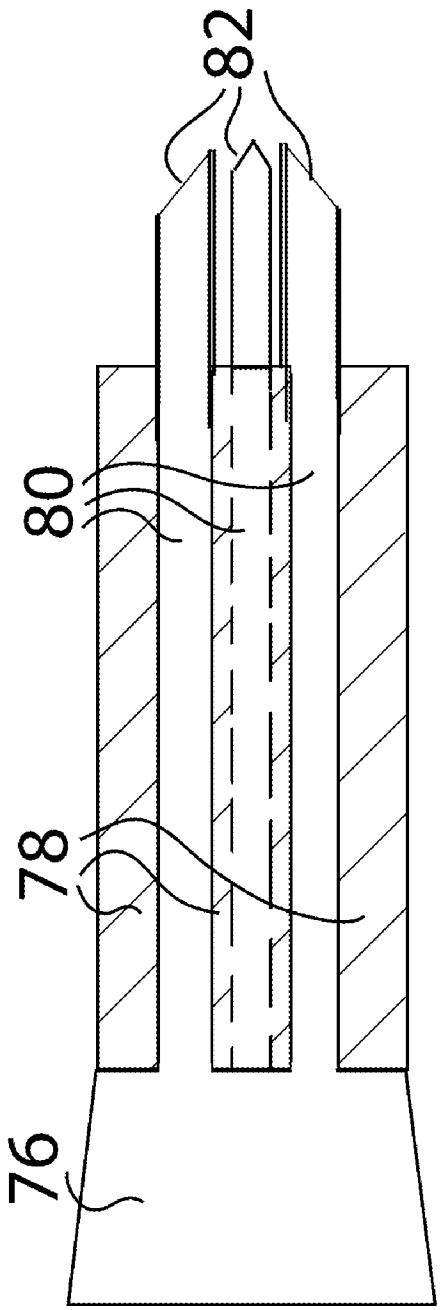


FIG. 13

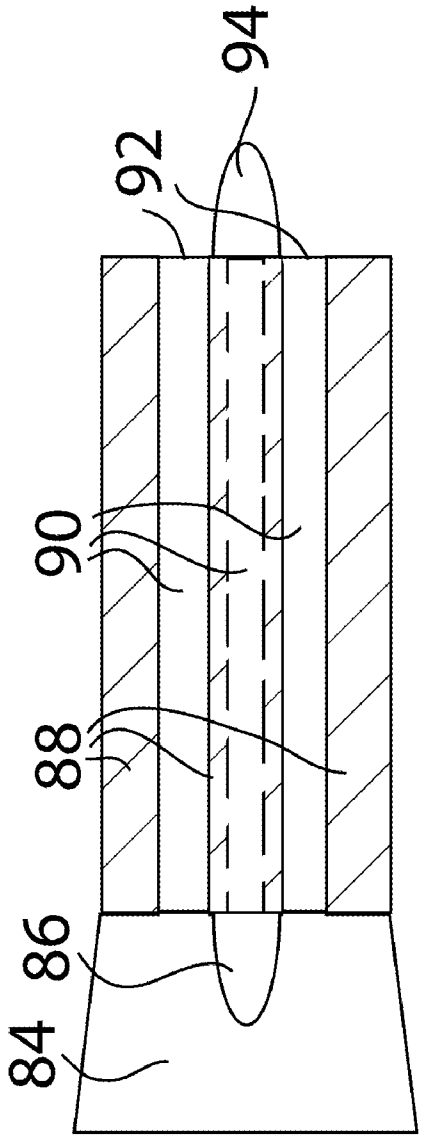


Fig. 14

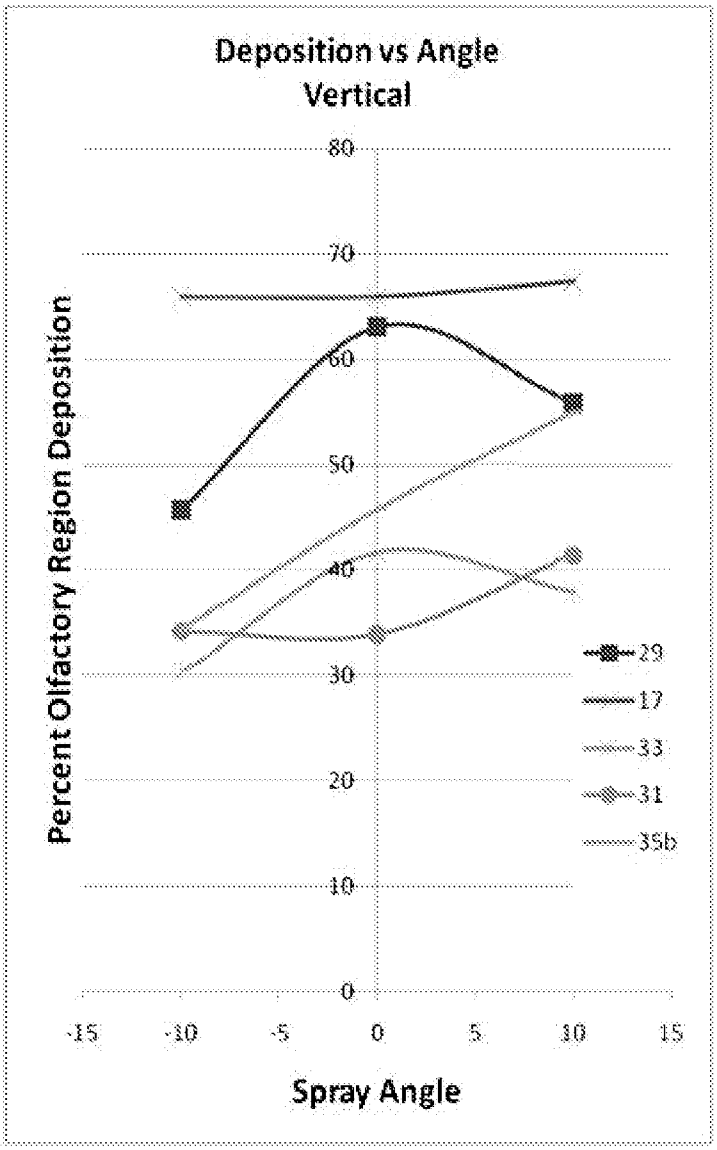

Deposition vs Angle
Vertical
Percent Olfactory Region Deposition
80
70
60
50
40
30
20
10
0
-15
-10
-5
0
5
10
15
Spray Angle
29
17
33
31
35b

FIG. 15

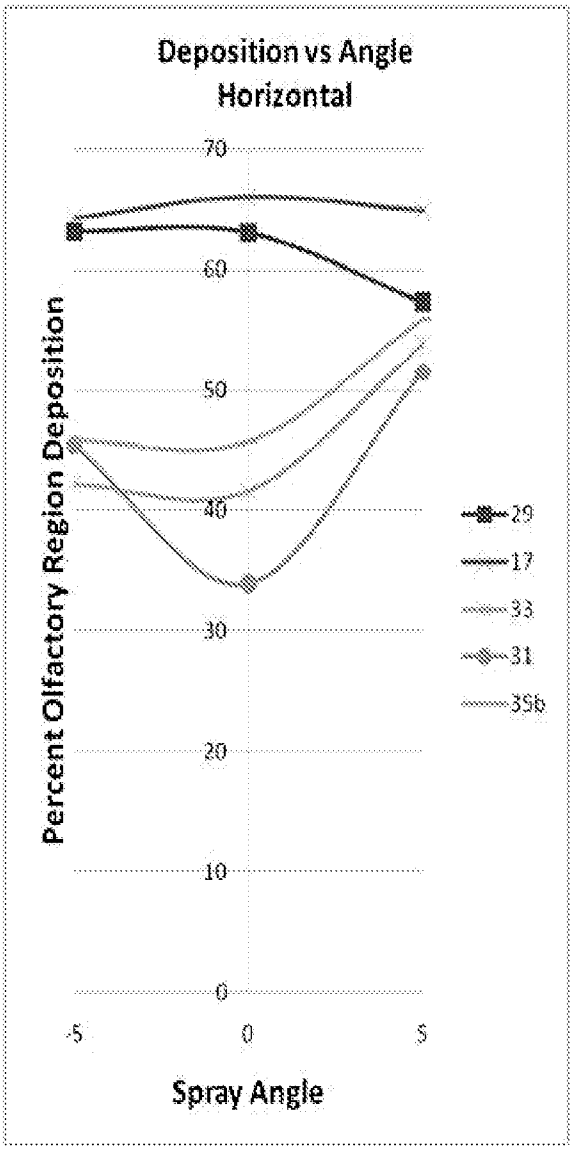

Deposition vs Angle
Horizontal
Percent Olfactory Region Deposition
70
60
50
40
30
20
10
0
-5
0
5
Spray Angle
29
17
33
31
35b

FIG. 16

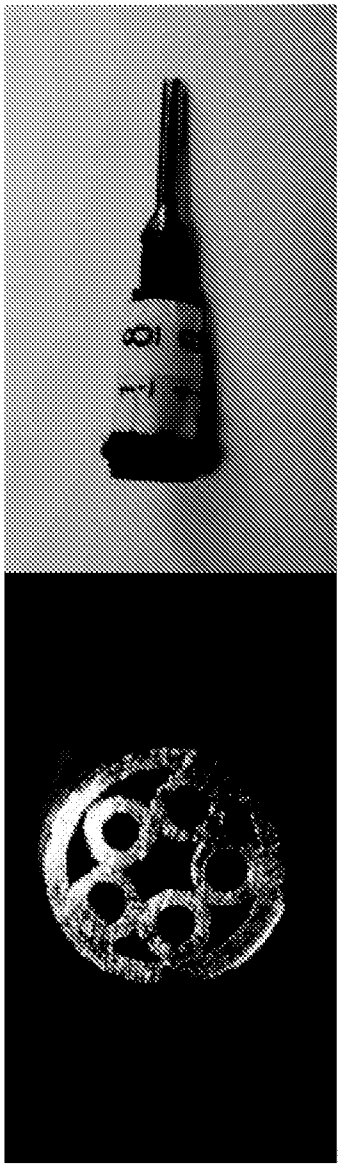


FIG. 17

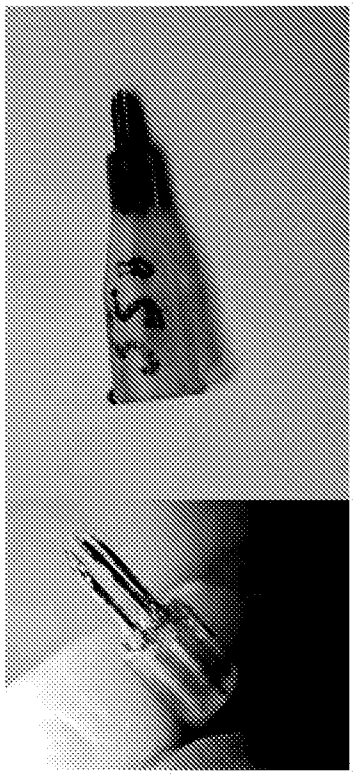


FIG. 18

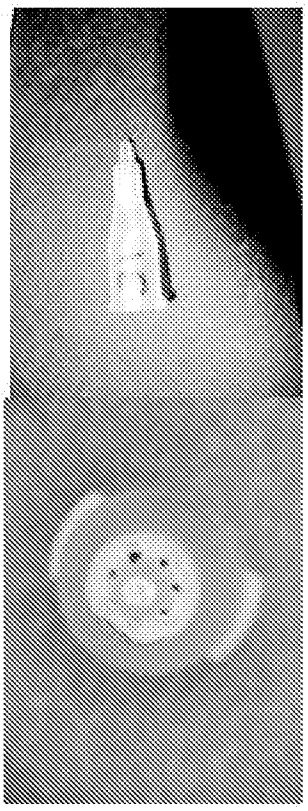


FIG. 19

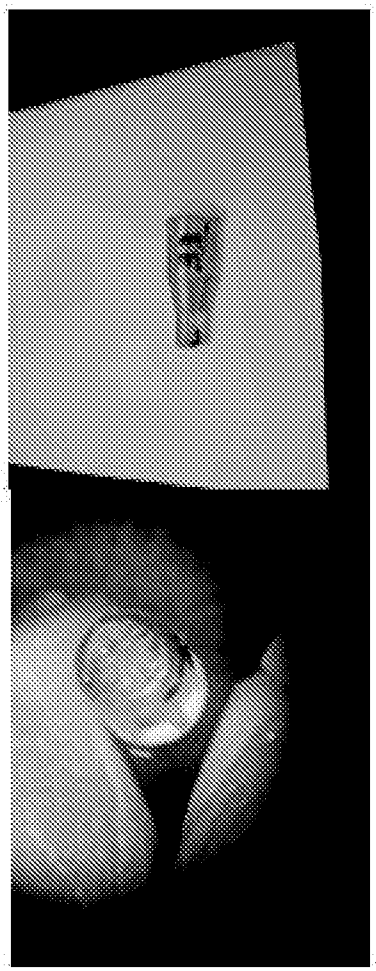


FIG. 20

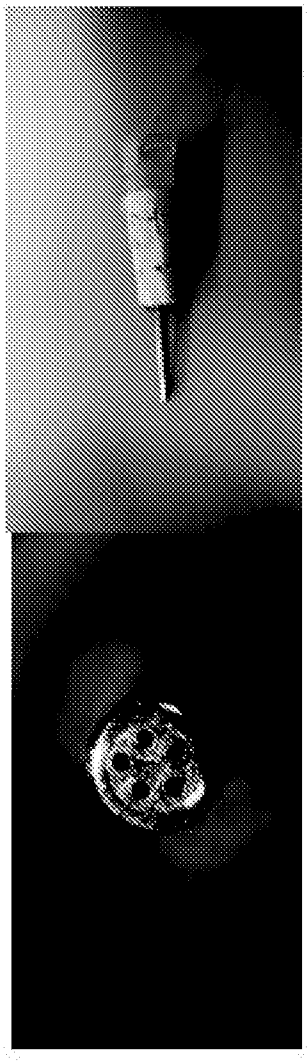


FIG. 21

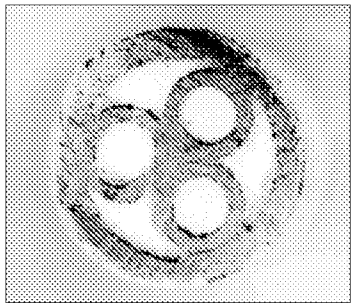
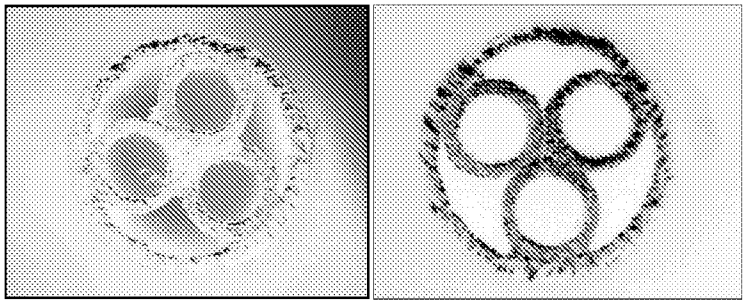
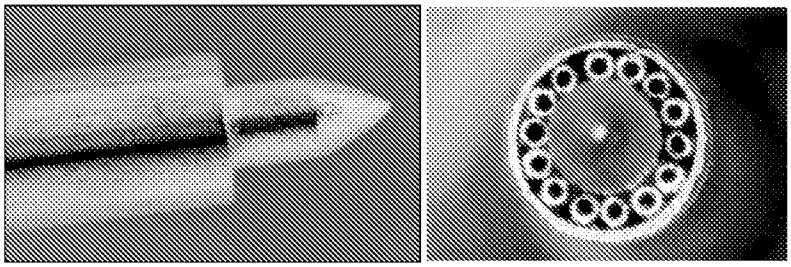


FIG. 22



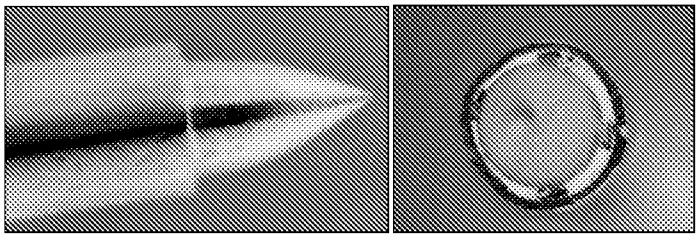
A B

FIG. 23



A B

FIG. 24



A B

FIG. 25

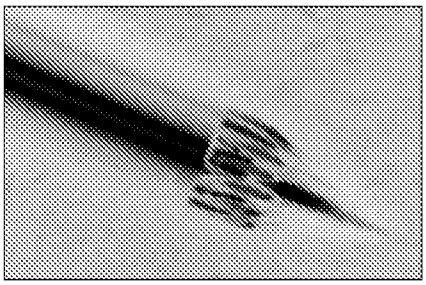


FIG.26

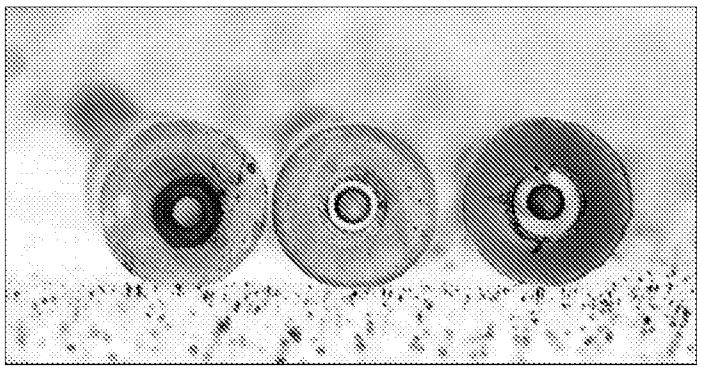


FIG. 27

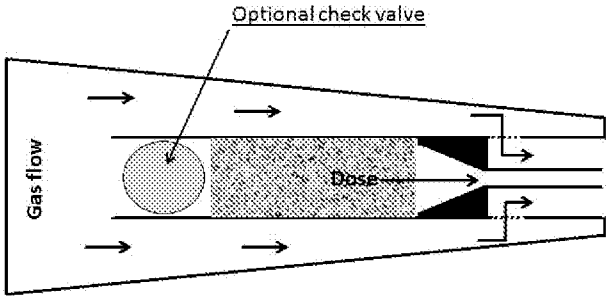


FIG. 28

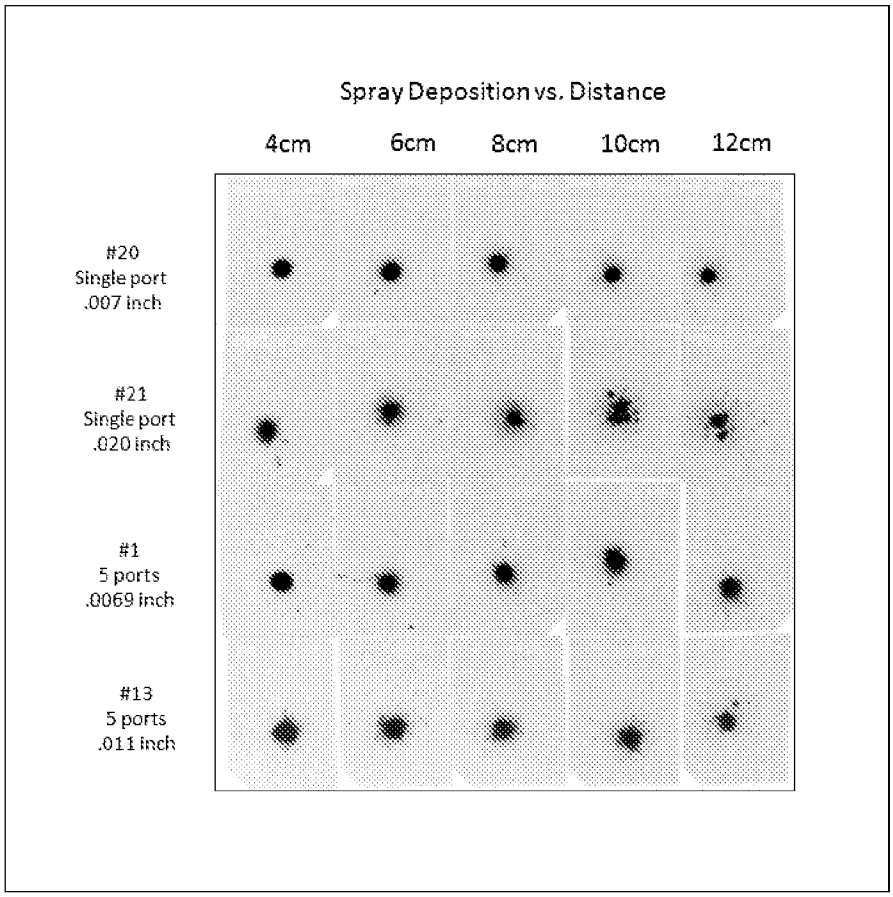

Spray Deposition vs. Distance
4cm
6cm
8cm
10cm
12cm
#20
Single port
.007 inch
#21
Single port
.020 inch
#1
5 ports
.0069 inch
#13
5 ports
.011 inch

FIG. 29

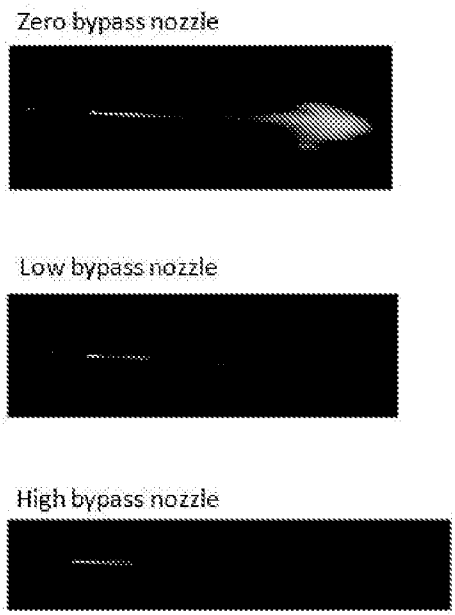


FIG. 30

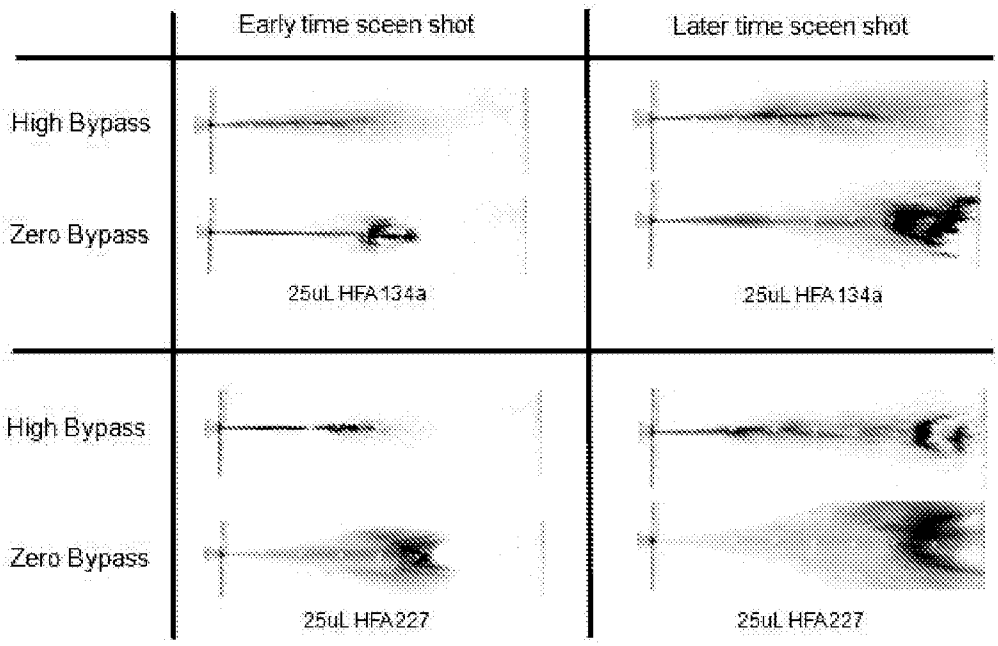

Early time sceen shot
Later time sceen shot
High Bypass
Zero Bypass
25uL HFA134a
25uL HFA134a
High Bypass
Zero Bypass
25uL HFA227
25uL HFA227

FIG.31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/37132

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - B05B 1/02 (2012.01)
USPC - 222/566
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): B05B 1/02 (2012.01)
USPC: 222/566

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 222/556, 575; 128/200.14; 239/86, 548, 550, 601

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB); Google Patents Advanced; Google Scholar
drug, nasal, delivery, nozzle, spray, atomize, nebulize, mist, medicine,medication, dipense, nose, nostril, channel, path, passage, tube, lumen, cannula, duct, dual, double, pair, two, side, coaxial, multiple, plural, propellent, aerosol, olfactory, check valve

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2004/0094146 A1 (Schiewe et al) 20 May 2004 (20.05.2004), entire document, especially Fig 1, 2, para [0005], [0118], [0119], [0122], [0124], [0167], [0168]	1, 2, 3, 4, 5, 14, 15, 16 --- 6-13, 17-25
Y	US 7,063,686 B2 (Mezzoli) 20 June 2006 (20.06.2006), especially Fig 4, Abstract, col 2, ln 35-44; col 3, ln 22-30, ln 62-67	6, 22, 23, 24, 25
Y	US 2010/0218759 A1 (Anderson et al) 02 September 2010 (02.09.2010), Fig 30a-30n, para [0004, [0005], [0226], [0227], [0228]	7-13
Y	US 2011/0048414 A1 (Hoekman et al) 03 March 2011 (03.03.2011), para [0006], [0033], [0060]	17-19
Y	US 7,819,342 B2 (Spallek et al) 26 October 2010 (26.03.2011), col 3, ln 14-24, col 3, ln 29-37	22-25
Y	US 2011/0045088 A1 (Tsutsui et al) 24 February 2011 (24.02.2011), Fig 1, para [0087]	25
Y	US 6,418,925 B1 (Genova et al) 16 July 2002 (16.07.2002), col 4, ln 48-50, col 6, ln 20-30	20, 21
A	US 3,949,939 B1 (Brown) 13 April 1976 (13.04.1976) Fig 2, Fig 7, check valve 80, col 3, ln 38-col 4, ln 4	25
A	US 7,875,001 B2 (Minotti) 25 January 2011 (25.01.2011), Fig 6, col 5, ln 27-36	1,15,22

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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	Date of mailing of the international search report
09 July 2012 (09.07.2012)	26 JUL 2012

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)