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DESCRIPTION

TECHNICAL FIELD

[0001] Embodiments disclosed herein relate to mouthpieces for inhalers for inhaling a medicament in aerosol form. Other embodiments herein relate to inhalers for inhaling a medicament in aerosol form.

BACKGROUND

[0002] Medicament administration via inhalation from a handheld inhaler is a well-known way of medicament administration to a patient. Some medicaments may be administered in powder form other medicament may be in liquid form which are administered as small droplets, both medicament forms may be referred to as aerosols. A patient puts a mouthpiece of the inhaler into his or her mouth and ejects a medicament dose, which is inhaled into the lungs of the patient.

[0003] Naturally, it is desirable that as much as possible of the medicament dose reaches the lungs of the patient. If the mouthpiece is directed towards the tongue or the teeth of the patient, an unnecessary large part of the medicament dose remain in the mouth of the patient and will not reach the lungs of the patient.

[0004] EP2381991 discloses an apparatus comprising a stepped mouthpiece for aerosol drug delivery. The apparatus aids in administering inhaled pharmaceutical aerosol to a patient. The apparatus is used in conjunction with an aerosol delivery device. The mouthpiece comprises steps on the top and bottom of the apparatus, which when used aid the patient in causing mandibular advancement, and opening of the mouth, also causing opening of the patient's airway, resulting in improved aerosol lung deposition. The steps are displaced horizontally in relation to each other when the mouthpiece is inserted into the mouth of a patient. The patient biting on the two steps causes the mandibular advancement. Document US2012/0240922 A1 discloses a mouthpiece with a tongue depressor that prevents aerosol collision with the tongue.

[0005] There is a need for alternative solutions, of administering a medicament in aerosol form to the lungs of a patient.

SUMMARY

[0006] The scope of the invention is as defined by the appended claims. It is an object to provide a mouthpiece which improves the administering of a medicament in aerosol form to the

lungs of a patient.

[0007] According to an aspect, this object is achieved by a mouthpiece for use with a handheld inhaler, the mouthpiece comprising a housing, wherein the housing comprises:

an inlet connectable to a medicament delivery device comprising a medicament container delivering an aerosol,

an outlet opening for the aerosol, and

a channel extending through the housing connecting the inlet and the outlet opening for directing the aerosol from the inlet to the outlet opening, wherein a plane extends through and along the channel, the plane defining on respective sides thereof an upper side and a lower side of the housing. An anterior portion of the housing is adapted to be placed in a mouth of a patient. The anterior portion of the housing is configured to direct the outlet opening upwardly in the oral cavity when the anterior portion is placed in the mouth of the patient.

[0008] Since the outlet opening is upwardly directed in the mouth of the patient, an aerosol from the inhaler being ejected into the mouth of the patient from the outlet opening of the mouthpiece is directed along the tongue of the patient, rather than towards the tongue. The aerosol will thus largely avoid sticking to the tongue and instead follow the oral cavity to the pharynx, the tracheal and the lungs of the patent. As a result, the above mentioned object is achieved.

[0009] It has been realized by the inventors that the mouthpiece as such may be configured to aid the patient in positioning the anterior portion in a mouth of a patient in a manner to improve the administering of an aerosol from an inhaler to the lungs of a patient.

[0010] In use, when the mouthpiece forms part of an inhaler, the plane may be upwardly inclined when the anterior portion is inserted into the mouth of the patient. Some medicaments may be administered in powder form other medicament may be in liquid form which are administered as small droplets, approximately 1 - 9 µm in diameter. Herein both medicament forms will be referred to as aerosols. A patient puts the anterior portion of the mouthpiece of the inhaler into his, or her, mouth and ejects via the outlet opening a medicament dose, which is inhaled into the lungs of the patient.

[0011] According to embodiments, the anterior portion of the housing may comprise a frusto-conical portion, the frusto-conical portion comprising a base extending substantially perpendicularly to the plane and a top extending substantially perpendicularly to the plane. The outlet opening may be arranged in the base, and the channel may extend through the top, between the inlet and the outlet opening. Accordingly, when placed in the mouth of the patient the wider base will be positioned farther into the oral cavity than the narrower top. Thus, a first portion of the outer surface of the frusto-conical portion may abut against the tongue, and a

second portion of the outer surface may abut against the palate behind the front teeth. Due the nature of the frusto-conical shape and the outlet opening being arranged in the base, the outlet opening will be directed upwardly into the oral cavity of the patient when abutting against the tongue and the palate directing an aerosol into the middle of the oral cavity. The smaller size at the top than at the base will encourage a patient to place his, or her, lips around the top of the frusto-conical portion. Thus, it may be ensured that the outlet opening is positioned sufficiently far into a mouth of the patient.

[0012] According to embodiments, the outlet opening may be smaller than the base of the frusto-conical portion, and the outlet opening may be centred in the base of the frusto-conical portion. In this manner, at the outlet opening, a distance may be created between the outlet opening and the tongue and a distance may be created between the outlet opening and the palate. Thus, the aerosol will be directed into the middle of the oral cavity.

[0013] According to embodiments, the base of the frusto-conical portion may be oval. In this manner the anterior portion may be positioned centrally in the oral cavity, seen in a lateral direction.

[0014] According to embodiments, an outer surface of the housing at the top of the frusto-conical portion may be provided with indentations and/or protrusions. In this manner a patient may sense the indentations and/or protrusions with his, or her, tongue, teeth, or lips to ensure that the entire anterior portion has been placed in the mouth of the patient. In particular, a patient may be instructed to sense the indentations and/or protrusions with the tip of his, or her, tongue. Thus, the tongue will be positioned out of the way of the outlet opening. Moreover, the mouthpiece will be angel away from the tongue.

[0015] According to the invention, groove portions adapted for placing lips of a patient there against may extend at least partially around the housing adjacent to the anterior portion. At least one groove portion on the upper side may extends closer to the outlet opening than at least one groove portion on the lower side. In this manner, when the patient places his or her lips in the groove portions on the upper side and on the lower side, the anterior portion will be placed in the mouth of the patient at an angle with the plane upwardly inclined to direct the outlet opening upwardly in the oral cavity.

[0016] According to embodiments, the groove portions may comprise convexly curved bottom surfaces. In this manner the groove portions are adapted for placing the lips of the patient there against.

[0017] According to a further aspect, the above mentioned object is achieved by a mouthpiece for use with a handheld inhaler, the mouthpiece comprising a housing, wherein the housing comprises:

an inlet connectable to a medicament delivery device comprising a medicament container delivering an aerosol,

an outlet opening for the aerosol, and

a channel extending through the housing connecting the inlet and the outlet opening for directing the aerosol from the inlet to the outlet opening, wherein a plane extends through and along the channel, the plane defining on respective sides thereof an upper side of the housing and a lower side of the housing. An anterior portion of the housing is adapted to be placed in a mouth of a patient. The outlet opening is placed closer to the upper side of the housing than to the lower side of the housing.

[0018] Since the outlet opening is placed closer to the upper side of the housing than to the lower side of the housing, an aerosol from the inhaler being directed into the mouth of the patient from the outlet opening of the mouthpiece is directed over the tongue of the patient, rather than towards the tongue. The aerosol will thus largely avoid sticking to the tongue and instead follow the oral cavity to the pharynx, the tracheal, and the lungs of the patient. As a result, the above mentioned object is achieved.

[0019] Also this aspect follows the line of thought along which the inventors have realized that the mouthpiece as such may be configured to aid the patient in placing the anterior portion in a mouth of a patient in a manner to improve the administering of an aerosol from an inhaler to the lungs of a patient.

[0020] According to embodiments, a channel-forming wall element of the channel may form at least a portion of an upper surface of the anterior portion on the upper side of the housing. A distance element positioned a distance from the channel may form at least a portion of a lower surface of the anterior portion on the lower side of the housing. In this manner the outlet opening may be placed closer to the upper side of the housing than to the lower side of the housing to create a distance between the tongue and the outlet opening.

[0021] According to embodiments, the mouthpiece may comprise a front surface extending substantially perpendicularly to the plane, wherein the outlet opening is arranged in the front surface.

[0022] According to a further aspect there is provided an inhaler comprising a mouthpiece according to any aspect or embodiment disclosed herein. The inhaler may be a handheld inhaler.

[0023] Further features and advantages will become apparent when studying the appended claims and the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Various aspects of embodiments, including their particular features and advantages, will be readily understood from the example embodiments discussed in the following detailed description and the accompanying drawings, in which:

Figs. 1a - 4 illustrate various mouthpieces for use with handheld inhalers, and

Figs. 5 and 6 illustrate handheld inhalers. The figures 2a and 2b disclose an embodiment of the invention. The remaining figures do not fall under the scope of the invention.

DETAILED DESCRIPTION

[0025] Aspects of example embodiments will now be described more fully. Like numbers refer to like elements throughout. Well-known functions or constructions will not necessarily be described in detail for brevity and/or clarity.

[0026] **Figs. 1a and 1b** illustrate a mouthpiece 2 for use with a handheld inhaler. The mouthpiece 2 forms a part of the inhaler, which is arranged to conduct an aerosol from a medicament container of the inhaler into an oral cavity of a patient. The mouthpiece 2 comprises a housing 4. The housing 4 comprises an inlet 6 and an outlet opening 8. The inlet 6 is connectable to a medicament delivery device of the inhaler comprising the medicament container delivering the aerosol. The mouthpiece 2 may for instance be connected to a body of an inhaler by means of a snap-fit connection, protrusions 9 of which are shown in Fig.1b. Through the outlet opening 8 the aerosol is adapted to be administered into the oral cavity to be inhaled into the lungs of the patient. A channel 10 extends through the housing 4 and connects the inlet 6 and the outlet opening 8. Thus, the channel 10 is adapted to direct the aerosol from the inlet 6 to the outlet opening. A plane 12 extends through and along the channel 10. The plane 12 defines on respective sides thereof an upper side 14 of the housing 4 and a lower side 16 of the housing 4. The outlet opening 8 is arranged at a first end portion 17 of the housing 4, between the upper side 14 and the lower side 16. The inlet 6 is arranged at a second end portion 19 of the housing 4, between the upper side 14 and the lower side 16. When the mouthpiece 2 is positioned to be placed in the mouth of the patient, the upper side 14 is arranged to face substantially upwardly and the lower side 16 is arranged to face substantially downwardly.

[0027] An anterior portion 18 of the housing 4 is adapted to be placed in the mouth of the patient. The anterior portion 18 of the housing 4 is configured to direct the outlet opening 8 upwardly in the oral cavity when the anterior portion 18 is placed in the mouth of the patient.

[0028] In these examples, the anterior portion 18 of the housing 4 comprises a frusto-conical portion 20. The frusto-conical portion 20 comprises a base 22 extending substantially perpendicularly to the plane 12 and a top 24 extending substantially perpendicularly to the plane 12. The outlet opening 8 is arranged in the base 22. The channel 10 extends through

the top 24, between the inlet 6 and the outlet opening 8.

[0029] Seen in a direction from the base 22 towards the top 24 along the plane 12, a wide housing portion 28 is arranged adjacent to the top 24. The anterior portion 18 thus, is terminated by the wide housing portion 28.

[0030] In a frusto-conical shape the base 22 is wider than the top 24. When placed in the mouth of the patient, the wide base 22 of the frusto-conical portion 20 will be positioned farther into the oral cavity than the narrow top 24. The patient places his or her lips around the top 24. A first portion of an outer surface of the frusto-conical portion 20 on the lower side 16 of the housing 4 will abut against the tongue of the patient. A second portion of the outer surface of the frusto-conical portion 20 on the upper side 14 of the housing 4 may abut against the palate behind the front teeth of the patient. Thus, the natural shape of the mouth cavity and the tongue of the patient will position the frusto-conical portion 20 with the plane 12 upwardly inclined, e.g. at an angle of 30 - 60 degrees to a vertical axis in the mouth of the patient. Accordingly, the outlet opening 8, being arranged in the base 22, will be directed upwardly into the oral cavity of the patient. The aerosol from the medicament delivery device will thus be administered into a middle portion of the oral cavity between the tongue and the palate. Thus, minimising the aerosol deposition on the tongue and/or the palate, helping the aerosol to reach the lungs of the patient.

[0031] The outlet opening 8 is smaller than the base 22 of the frusto-conical portion 20. The outlet opening 8 is centred in the base 22 of the frusto-conical portion. The distances created between the tongue and the outlet opening 8 and the distance created between the palate and the outlet opening 8 by the outlet opening 8 being smaller than the base 22 also aids in administering the aerosol in the middle portion of the oral cavity. Thus, minimising the aerosol deposition on the tongue and/or the palate, helping the aerosol to reach the lungs of the patient.

[0032] The base 22 of the frusto-conical portion 20 is oval. An outer surface of the housing 4 at the top 24 of the frusto-conical portion 20 is provided with indentations and/or protrusions 26. A patient may sense the indentations and/or protrusions 26 with his or her tongue, teeth, or lips to ensure that the entire anterior portion 18 has been placed in the mouth.

[0033] The following dimensions are mentioned purely as an example. The mouthpiece 2 may have a length of 10-70 mm. The length of the anterior portion 18 may be 10-40 mm. The large diameter of the base 22 may be 25-40 mm and the small diameter of the base 22 may be 15 - 25 mm. The large diameter of the top 24 may be 20-30 mm and the small diameter of the top 24 may be12 - 20 mm. The diameter of the wide portion 28 may be15-35 mm. The diameter of the outlet opening 8 may be 14-25mm.

[0034] **Figs. 2a and 2b** illustrate embodiments of a mouthpiece 2 for use with a handheld inhaler. The mouthpiece 2 forms a part of the inhaler, which is arranged to conduct an aerosol from a medicament container of the inhaler into an oral cavity of a patient. Some features are

common with the examples of Figs. 1a and 1b.

[0035] Thus again, the mouthpiece 2 comprises a housing 4. The housing 4 comprises an inlet 6 and an outlet opening 8. A channel 10 extends through the housing 4 and connects the inlet 6 and the outlet opening 8. A plane 12 extends through and along the channel 10. The plane 12 defines on respective sides thereof an upper side 14 and a lower side 16 of the housing 4. When the mouthpiece 2 is positioned to be placed in the mouth of the patient, the upper side 14 is arranged to face substantially upwardly and the lower side 16 is arranged to face substantially downwardly. An anterior portion 18 of the housing 4 is adapted to be placed in the mouth of the patient. The anterior portion 18 of the housing 4 is configured to direct the outlet opening 8 upwardly in the oral cavity when the anterior portion is placed in the mouth of the patient.

[0036] In these embodiments, groove portions 30, 32 extend at least partially around the housing 4 adjacent to the anterior portion 18. The groove potions 30, 32 are adapted for placing lips of the patient there against. At least one groove portion 30 on the upper side 14 of the housing 4 extends closer to the outlet opening 8 than at least one groove portion 32 on the lower side 16 of the housing 4. The groove portions 30, 32 comprise convexly curved bottom surfaces 33.

[0037] When the patient places his or her lips in the groove portions 30, 32 on the upper side 14 and on the lower side 16, the anterior portion 18 will be placed in the mouth of the patient with the plane 12 upwardly inclined to direct the outlet opening 8 upwardly in the oral cavity. The plane 12 may be placed at an angle of 30 - 60 degrees with a vertical axis. The groove portions 30, 42 may extend across the plane 12 at an angle α of approximately 30 - 45 degrees. Thus, the anterior portion 18 is longer on the lower side 16 than on the upper side 14.

[0038] The following dimensions are mentioned purely as an example. The mouthpiece 2 may have a length of 20-50 mm. The length of the anterior portion 18 may be 10-20 mm at the upper side 14 and 20-40 mm at the lower side 16. The diameter of the outlet opening 8 may be 14-24 mm. The radius of the convexly curved bottom surfaces 33 of the groove portions 30, 32 may be 5-10 mm.

[0039] **Figs. 3a and 3b** illustrate examples of a mouthpiece 2 for use with a handheld inhaler. The mouthpiece 2 forms a part of the inhaler, which is arranged to conduct an aerosol from a medicament container of the inhaler into an oral cavity of a patient. Some features are common with the disclosure of Figs. 1a - 2b.

[0040] Thus again, the mouthpiece 2 comprises a housing 4. The housing 4 comprises an inlet 6 and an outlet opening 8. A channel 10 extends through the housing 4 and connects the inlet 6 and the outlet opening 8. A plane 12 extends through and along the channel 10. The plane 12 defines on respective sides thereof an upper side 14 and a lower side 16 of the housing 4. When the mouthpiece 2 is positioned to be placed in the mouth of the patient, the

upper side 14 is arranged to face substantially upwardly and the lower side 16 is arranged to face substantially downwardly. An anterior portion 18 of the housing 4 is adapted to be placed in the mouth of the patient.

[0041] In these examples, the outlet 8 opening is placed closer to the upper side 14 of the housing 4 than to the lower side 16 of the housing 4. Thus, an aerosol from the inhaler being directed into the mouth of the patient from the outlet opening 8 of the mouthpiece 2 is directed over the tongue into the oral cavity to improve the administering of the aerosol from the inhaler to the lungs of the patient.

[0042] A channel-forming wall element 34 of the channel 10 forms at least a portion of an upper surface 36 of the anterior portion 18 on the upper side 14 of the housing 4. A distance element 38 is positioned at a distance from the channel 10 and forms at least a portion of a lower surface 40 of the anterior portion 18 on the lower side 16 of the housing 4. Accordingly, the outlet opening 8 is placed closer to the upper side 14 of the housing 4 than to the lower side 16 of the housing 4 to create a distance between the tongue of the patient and the outlet opening 8.

[0043] The distance element 38 extends outside the outlet opening 8 seen along the plane 12. The distance element 38 connects to the channel-forming wall element 34 at a middle portion of the channel 10.

[0044] The following dimensions are mentioned purely as an example. The mouthpiece 2 may have a length of 10-70 mm. The length of the anterior portion 18 may be 10-40 mm. The diameter of the outlet opening 8 may be 14-24 mm. The distance between the centre of the channel 10, i.e. the plane 12, to the lower surface 40 may be 10-20 mm.

[0045] **Fig 4** illustrates examples of a mouthpiece 2 for use with a handheld inhaler. The mouthpiece 2 forms a part of the inhaler, which is arranged to conduct an aerosol from a medicament container of the inhaler into an oral cavity of a patient. The mouthpiece 2 according to these examples is similar to the mouthpiece according to the examples of Figs. 3a - 3b. The main difference lies in that the distance element 38 is shaped differently to create an oval shaped end of the anterior portion 18 at the outlet opening 8. The distance element 38 does not extend beyond the outlet opening 8. However again, the distance element 38 is positioned a distance from the channel 10 and forms at least a portion of a lower surface 40 of the anterior portion 18 on the lower side 16 of the housing 4.

[0046] Fig. 5 illustrates a handheld inhaler 50 according to examples. The inhaler 50 comprises a mouthpiece 2, an inhaler body 52, and a medicament container holder 54. The inhaler body 52 and the medicament container holder 54 may form a medicament delivery device. A patient uses the inhaler 50 by placing an anterior portion 18 of the mouthpiece 2 into his or her mouth, and pressing the medicament container holder 54 towards the inhaler body 52 while inhaling to eject a dose of medicament in aerosol form to be administered via the mouthpiece 2 into the mouth and the lungs of the patient.

[0047] The mouthpiece 2 according to these examples is similar to the mouthpiece according to the examples of Figs. 3a, 3b, and 4. The main difference lies in that the mouthpiece 2 comprises a front surface 56 extending substantially perpendicularly to the plane 12. The outlet opening 8 is arranged in the front surface 56. Again, a distance element 38 is positioned at a distance from the channel 10 forming at least a portion of a lower surface 40 of the anterior portion 18 on the lower side 16 of the housing 4 of the mouthpiece 2.

[0048] **Fig. 6** illustrates a handheld inhaler 50. The inhaler 50 comprises a mouthpiece 2, an inhaler body 52, inside which a medicament container is arranged, and an energy supplying arrangement 60. The inhaler body 52 and the energy supplying arrangement 60 may form a medicament delivery device. The energy supplying arrangement 60 is loaded by a patient prior to administering an aerosol from the inhaler 50. The patient places an anterior portion 18 of the mouthpiece 2 into his or her mouth, and releases the energy supplying arrangement 60 by pressing the release button 62. At the same time the patient inhales. Thus, a dose of medicament in aerosol form is ejected from the medicament container by the energy supplying arrangement 60 and administered via the mouthpiece 2 into the mouth and the lungs of the patient. The energy supplying arrangement 60 may be reusable. The inhaler body 52 and the mouthpiece 2 may be disposable.

[0049] The mouthpiece 2 illustrated in Fig. 6 corresponds to the examples illustrated in Figs.1a and 1 b. Mouthpieces 2 according to other disclosure disclosed herein may alternatively be used.

[0050] Similarly, mouthpieces 2 disclosed in Figs. 1a - 4 may alternatively be used in the inhaler 50 disclosed in Fig. 5. This invention should not be construed as limited to the embodiments set forth herein. A person skilled in the art will realize that different features of the described embodiments may be combined to create embodiments other than those described herein, without departing from the scope of protection, as defined by the appended claims. The mouthpieces 2 disclosed herein may be manufactured from plastic material, such as polymers. Although the invention has been described with reference to example embodiments, many different alterations, modifications and the like will become apparent for those skilled in the art. Therefore, it is to be understood that the foregoing is illustrative of various example embodiments and that the invention is defined only the appended claims.

[0051] As used herein, the term "comprising" or "comprises" is open-ended, and includes one or more stated features, elements, steps, components or functions but does not preclude the presence or addition of one or more other features, elements, steps, components, functions or groups thereof.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not

form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

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- US20120240922A1 [0004]

PATENTKRAV

1. Mundstykke (2) til anvendelse med en håndholdt inhalator, hvilket mundstykke (2) omfatter et hus (4), hvor huset (4) omfatter:
et indløb (6), der kan kobles til en lægemiddelafgivelsesindretning omfattende en lægemiddelbeholder, der afgiver en aerosol,
en udløbsåbning (8) for aerosolen, og
en kanal (10), som strækker sig gennem huset (4) og forbinder indløbet (6) og udløbsåbningen (8) til at sende aerosolen fra indløbet (6) til udløbsåbningen (8),
hvor en plan (12) strækker sig gennem og langs kanalen (10), hvilken plan (12) på hver side deraf definerer henholdsvis en overside (14) og en underside (16) af huset (4), og hvor en forreste del (18) af huset (4) er indrettet til anbringelse i munden på en patient, hvor den forreste del (18) af huset (4) er indrettet til at rette udløbsåbningen (8) opad i mundhulen, når den forreste del (18) anbringes i patientens mund,
hvor rilledele (30, 32) beregnet til anbringelse af en patients læber imod disse strækker sig mindst delvis omkring huset (4) nær den forreste del (18), og hvor mindst én rilledel (30) på oversiden (14) strækker sig tættere til udløbsåbningen (8) end mindst én rilledel (32) på undersiden (16).

2. Mundstykke (2) ifølge krav 1, i hvilket den forreste del (18) af huset (4) omfatter en keglestubformet del (20), hvilken keglestubformet del (20) omfatter en bund (22), der strækker sig hovedsageligt vinkelret på planen (12), og en top (24), der strækker sig hovedsageligt vinkelret på planen (12), i hvilket udløbsåbningen (8) er anbragt i bunden (22), og i hvilket kanalen (10) strækker sig gennem toppen (24) mellem indløbet (6) og udløbsåbningen (8).

3. Mundstykke (2) ifølge krav 2, i hvilket udløbsåbningen (8) er mindre end bunden (22) af den keglestubformede del (20), og i hvilket udløbsåbningen (8) er centreret i bunden (22) af den keglestubformede del (20).

4. Mundstykke (2) ifølge krav 2 eller 3, i hvilket bunden (22) af den keglestubformede del (20) er oval.

5. Mundstykke (2) ifølge ethvert af kravene 2-4, i hvilket en ydre overflade af huset (4) ved toppen (24) af den keglestubformede del (20) er forsynet med indskæringer og/eller fremspring (26).

6. Mundstykke (2) ifølge krav 1, i hvilket rilledelene omfatter konvekst krummede bundflader (33).

7. Inhalator (50) omfattende et mundstykke (2) ifølge ethvert af kravene 1-6.

DRAWINGS

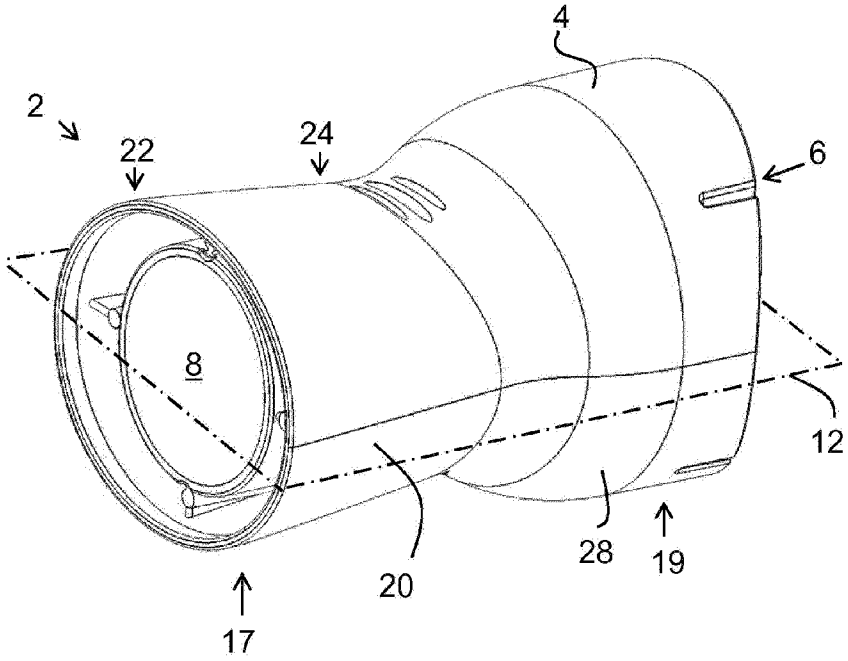

Fig. 1a

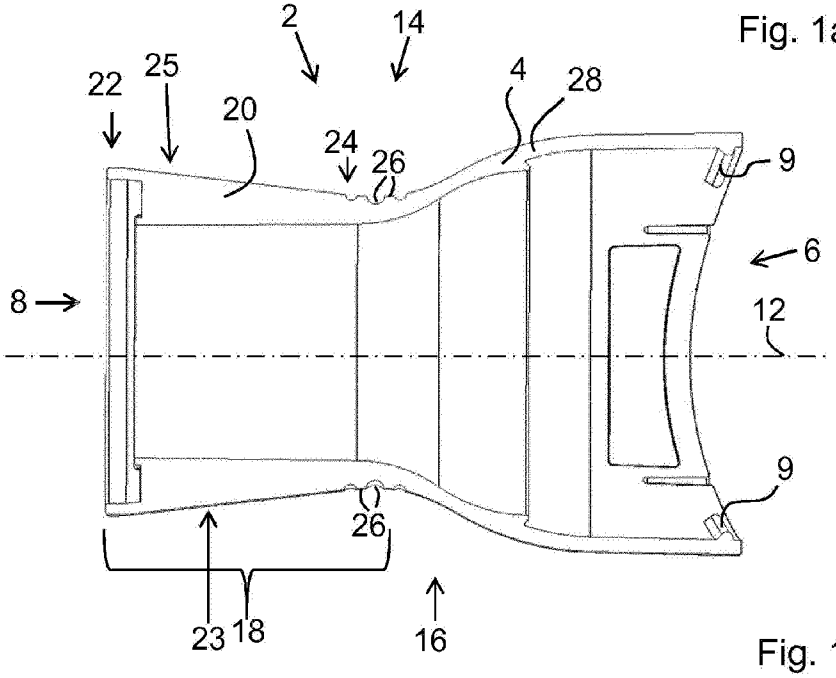

Fig. 1b

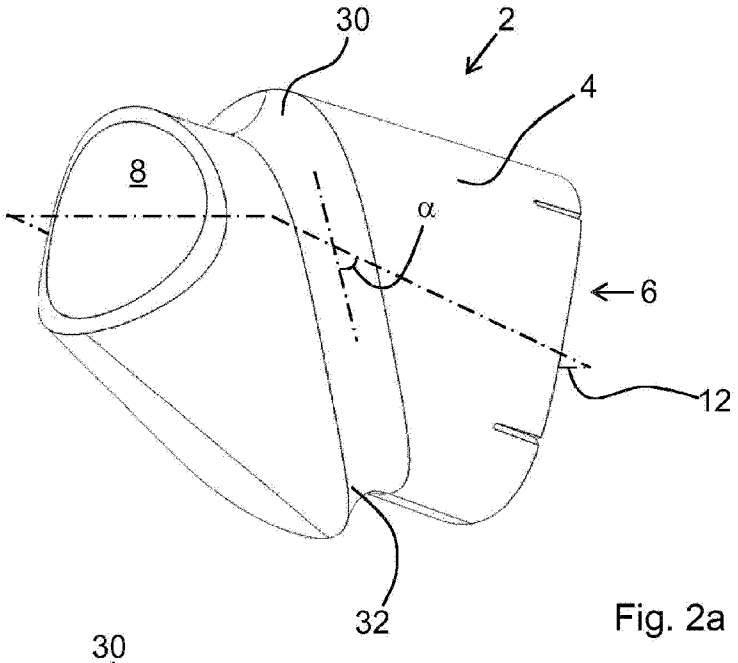

Fig. 2a

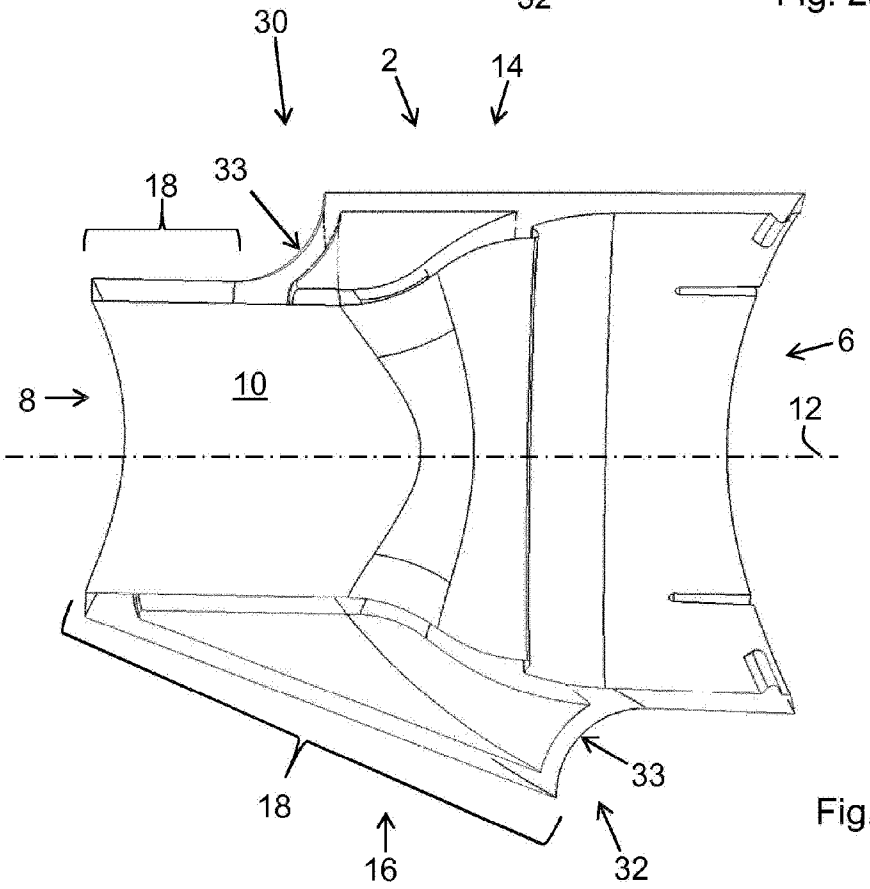

Fig. 2b

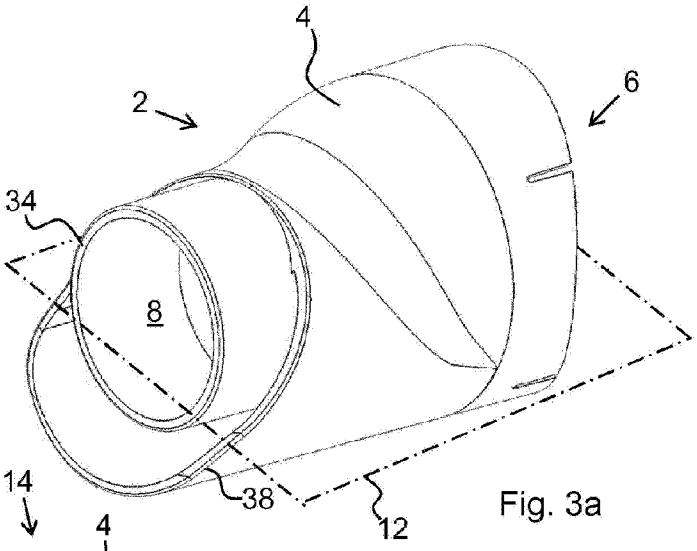

Fig. 3a

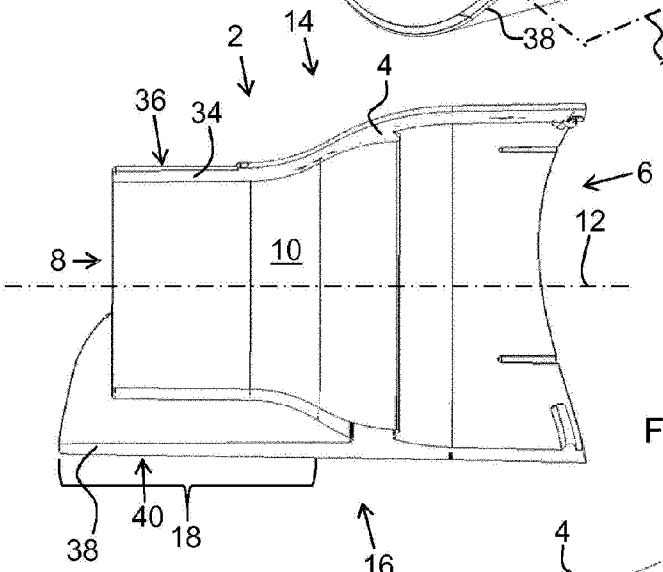

Fig. 3b

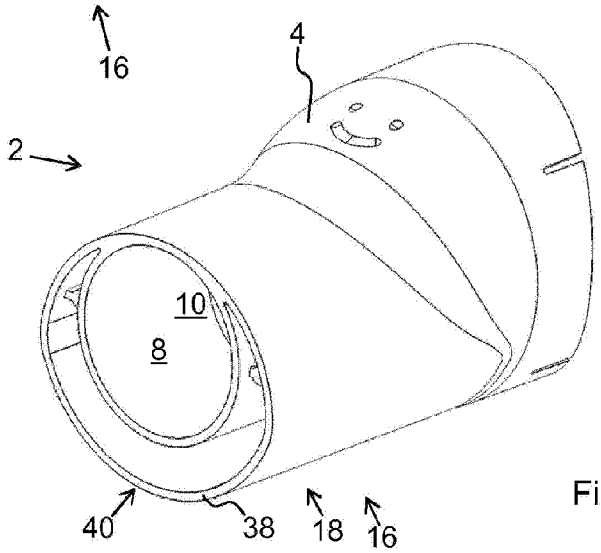

Fig. 4

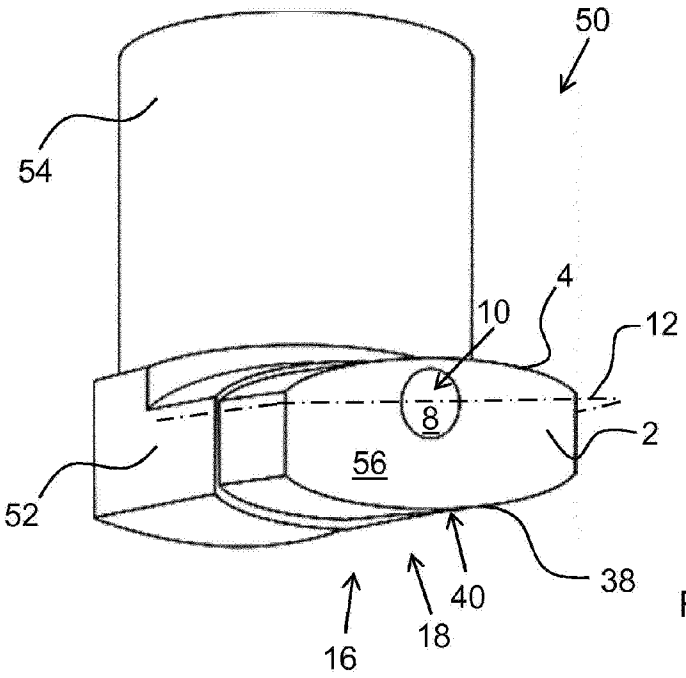

Fig. 5

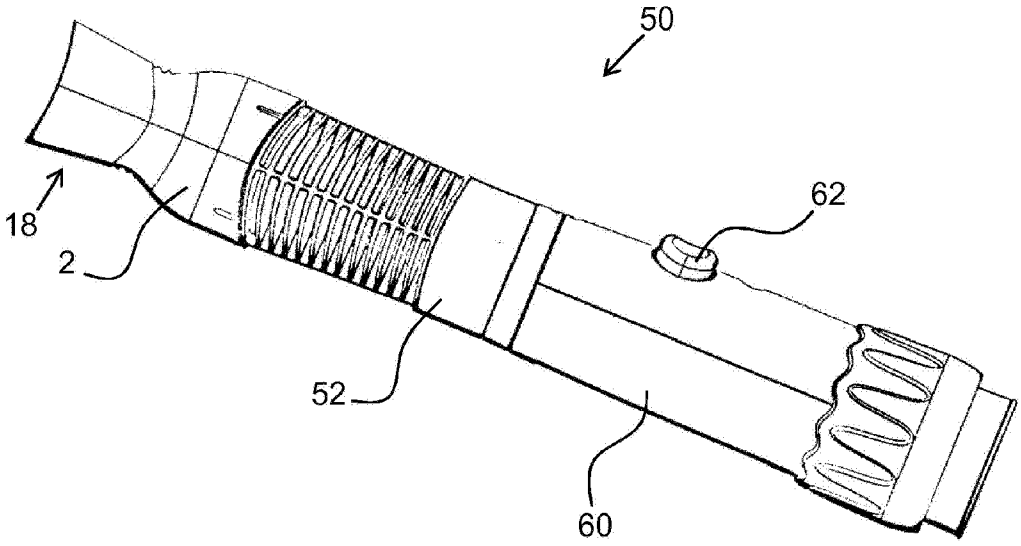

Fig. 6