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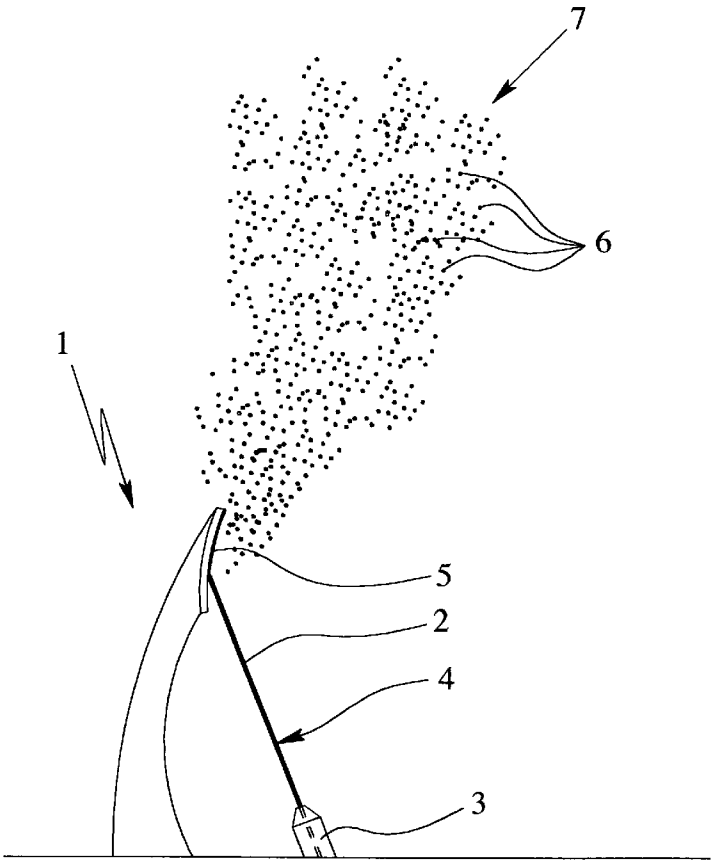
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(54) Title: METHOD AND DEVICE FOR ATOMISING LIQUID



(57) Abstract: A method and a device for the atomisation of a liquid are proposed. A liquid jet is directed onto a hot contact surface, in particular a deflecting surface, so that a part of the liquid is vaporised. The non-vaporised liquid is atomised into small droplets that form an aerosol. A method for the production of such a device is also proposed.

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Method and Device for Atomising Liquid

The present invention relates to a method and a device for atomising (nebulising) a liquid, in particular a liquid medicament formulation, as well as a method for the production of such a device.

In the atomisation of a liquid medicament formulation the object is to convert an as accurately-defined amount of active constituent as possible into an aerosol for inhalation. The aerosol should be characterised by a small mean value of the droplet size with a narrow droplet size distribution and by a small momentum (low propagation rate).

The expression "medicament formulation" used in the present invention is understood to include, apart from medicaments, also therapeutic agents or the like, in particular therefore all types of agents for inhalation. The present invention is however not restricted to the atomisation of agents for inhalation, but in particular may also be employed for cosmetic agents or other liquids and possibly also for suspensions or the like, even if the following description is primarily directed to the preferred atomisation of a medicament formulation for inhalation.

The term "aerosol" is understood in the context of the present invention to mean a preferably nebulous collection of a large number of droplets of the atomised liquid with preferably a substantially non-directed (random) and/or broad spatial distribution of the directions of movement and preferably with low velocities of the droplets.

WO 92/04065 A1, WO 03/047763 A1, EP 0 471 323 A1, EP 0 653 218 A1 and US 5,241,954 A disclose nebulisers for liquids for inhalation purposes. The liquid is in each case mixed with a gas stream and directed onto a deflecting surface to effect nebulisation. This is complicated and is not always effective, and in particular the droplet size may vary greatly.

WO 92/19383 A1 discloses an atomisation of a liquid without an additional gas stream or compressed air. A liquid jet is directed onto a conical deflecting

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surface for the atomisation, so that the liquid is atomised in a plane transverse to the axis of the cone, in order to generate droplets with a diameter of less than 10 µm for inhalation purposes. It is difficult to generate an aerosol in this way having a defined droplet size and a narrow, constant droplet size distribution.

US 5,261,949 A relates to a method of producing an atomized liquid to be conveyed in a stream of a carrier gas and to an apparatus for implementing the method. A liquid mist for being conveyed by a carrier gas stream is produced from a liquid by atomizing the liquid into the carrier gas stream in the form a collection of droplets, deflecting the collection of droplets in the carrier gas stream at a deflection region, separating droplets in the collection of droplets which exceed a maximum size from the carrier gas stream, collecting at least a part of the separated droplets on at least one heatable contact surface, and at least partially vaporizing them into the carrier gas stream. This method requires a first aerosolization of the liquid in a spray of droplets and a second aerosolization of the larger droplets by means of the heatable contact surface. A further disadvantage is that a carrier gas stream is necessary. This makes it difficult or even impossible to generate an aerosol with the desired characteristics, in particular a low propagation rate. Moreover, the method is not suitable for inhalers to generate a defined aerosol of a medical formulation.

FR 2 682 049 A1 relates to a device for generating a mixture of air and vapor of hydrogen peroxide. The device comprises a nozzle for atomizing the liquid hydrogen peroxide pneumatically and generating a mixture of air and droplets of hydrogen peroxide. This aerosol is directed onto a contact surface heated to about 200° C. Thus, the droplets of hydrogen peroxide shall be vaporized so that vapor of hydrogen peroxide is generated.

GB 2 214 088 A relates to a heated nebulizer system for producing a humidified and heated breathing gas to be inhaled by a patient undergoing inhalation therapy. Pressurized oxygen is discharged via a nozzle and generates an aerosol spray of liquid water and ambient air. This aerosol is directed in a conical pattern onto an annular heated surface upon which the aerosol impinges. The heated surface volatilizes at least a portion of the

aerosol while allowing the remainder to coalesce and return through a port to a reservoir of the liquid water. Thus, it is desired to generated water vapor so that humidified and heated gas can be breathed.

GB 744,547 A relates to a method for thermal production of an aerosol of an insecticide, such as DDT, bactericide or the like active material in which a solution or dispersion of the active material in a more volatile vehicle is caused to impinge onto a surface, heated to a temperature above the boiling point of the vehicle. As the result of the consequent rapid boiling of the vehicle, the latter assumes a state in which the bulk phase of the boiling material is separated from the hot surface by a layer of vapor of the vehicle. The liquid is discharged either between two heated plates or though a conduit surrounded by the heating jacket. This method is not suitable for generating a defined aerosol with the desired characteristics, in particular with low propagation rate and/or small particle size.

The Canon company markets under the reference number "i850" a printer operating according to the so-called bubble jet principle. The printer comprises a plurality of nozzle openings with a diameter of 10 µm for ejecting ink droplets with a volume of 2 pl, i.e. with a diameter of about 12 µm. Liquid chambers in which the ink is vaporised by means of an electrothermal element are associated with the nozzle openings. The change in volume occurring on vaporisation leads to the ejection of the ink droplets through the nozzle openings. In order to achieve the desired resolution of for example 4,800 dpi, the ink droplets are ejected at high velocity (10 m/sec or more) in a specific direction through a nozzle.

In the bubble jet principle a complicating factor is that the ejection of the individual droplets and accordingly the renewed vaporisation of ink have to be controlled individually for the individual nozzles, in order to achieve a desired print image. Apart from the timing, the site and momentum of the formed droplet are important in the bubble jet principle. For this reason the print head comprises a plurality of individual heaters, ink chambers and nozzles, in which each configuration of heater, ink chamber and nozzle can generate and eject individual droplets only in succession. Such a print head is complicated and expensive to manufacture. A very large number of nozzles is required to

achieve the droplet rate that is normally necessary for an inhaler. In addition there is the danger of the undetected stoppage or blockage of individual nozzles as well as the failure of individual heating elements, for example due to deposits or the like. Moreover, when the bubble jet principle is employed for medicament formulations further undesirable effects, such as a build-up of active constituent, reactions of the active constituent, or the like, may occur.

The object of the present invention is to provide a method and a device for atomising a liquid as well as a method for the production of such a device, so as to enable an effective atomisation of the liquid and the generation of an aerosol in a simple and effective way, in particular where the aerosol has a small droplet size of on average preferably less than 10 µm diameter, a narrow and constant droplet size distribution and/or a low propagation rate, and/or so as to enable a simple and inexpensive production.

The above object is achieved by a method according to claim 1 or a device according to claim 25, or by a method according to claim 47. Advantageous modifications are the subject matter of the sub claims.

A basic idea of the present invention consists in vaporising a small proportion of the liquid in order to atomise the remaining liquid into small droplets, more specifically, in contrast to the aforementioned bubble jet principle, in a non-directed manner, i.e. at least with a very broad spatial velocity distribution of the droplets, in order thereby to generate an aerosol. This enables an aerosol having the desired properties to be generated in a very simple and effective manner.

According to the present invention, the liquid is directed in the form of a preferably free jet onto a hot contact surface, in particular a warmed or heated deflecting surface. When the jet strikes the surface a small proportion of the liquid undergoes a spontaneous transition from the liquid to the gaseous phase. On account of the spontaneous vaporisation of the liquid occurring above a certain temperature, a very high pressure is produced that ejects or dissolves out, as droplets, a specific amount of liquid from the jet. On the one hand only a small part of the incident liquid is thereby vaporised. On the other hand the residence time of the non-vaporised liquid is very short, which

means that the non-vaporised liquid is scarcely heated. This last fact is of great advantage, in particular in the case of heat-sensitive medicament formulations. In contrast to conventional deflecting surfaces the incident velocity is not, or is only slightly, relevant for the atomisation; instead, the energy for the atomisation is primarily provided by the vapour pressure of the vaporised liquid and accordingly the atomisation is determined at least substantially by the temperature of the contact element. The velocity of the incident liquid, in particular the jet, on the other hand primarily determines the aerosol stream and the droplet rate.

In the present invention, the term "jet" preferably means that the liquid is discharged or ejected in a continuous manner, in particular like a column of liquid. Therefore, such a jet is preferably neither a spray of droplets nor an aerosol, although the jet (column of liquid) may be interrupted and may consist of multiple segments of liquid or the like.

Most preferably, any aerosolization of the liquid is not necessary and not provided before the partial vaporisation on the contact surface. Instead, the liquid is directed only in the form of a preferably focused or defined jet onto the hot or heated contact surface. Thus, a very simple, inexpensive and/or compact construction is possible.

In particular, in contrast to the previously known mechanical atomisation methods, in the solution according to the present proposal substantially lower pressures are sufficient to deliver the liquid. The atomisation *per se* takes place in fact preferably at least substantially due to the vaporisation and, most preferably, only by the vaporisation. The phase transition from the liquid to gaseous state leads in fact to a sharp increase in volume, in the case of water by a factor of ca. 1700. This sudden change in volume leads to a marked increase in kinetic energy and permits a spontaneous splitting of the liquid into individual, very small droplets.

In addition it is sufficient to vaporise only a small proportion of the liquid in order to achieve the desired atomisation effect. Thus, an aerosol having the desired properties, in particular a small droplet size, narrow and constant

droplet size distribution and/or low propagation rate, can be generated very simply and effectively.

In particular the atomised liquid droplets together with the ambient atmosphere form the aerosol. The liquid is accordingly preferably gas-free, i.e. consists only of a liquid phase and in particular contains no dissolved propellant gas or the like.

Preferably small amounts of the liquid are atomised in succession. This permits an at least substantially uniform distribution of the energy in the respective amount of liquid to be atomised, and thereby produces a very uniform, narrow size distribution of the liquid droplets formed in the atomisation.

The successive atomisation and discharge of small amounts of the liquid, in particular doses of a medicament formulation, e.g. of 10 to 100 µl, may take place continuously or discontinuously. Preferably a continues jet with a small diameter is generated from the liquid, which is then atomised by partial evaporation of the liquid to generate the desired aerosol. However, the jet may also be interrupted.

Alternatively or in addition, the aforementioned small amounts of liquid may also be atomised in parallel, i.e. over parallel flow paths, jets and/or at separate locational regions, and in particular simultaneously.

Particularly preferably the liquid is atomised into droplets without using side walls. This is compatible with the formation of a nebulous aerosol having a preferably low propagation rate, in particular a quasi-stationary aerosol cloud.

The phase transition and vaporisation takes place on contact with the contact or deflecting surface, preferably without any delay in boiling. The temperature of the contact element and the contact surface is for this purpose preferably significantly greater than the vaporisation temperature of the liquid or of a constituent of the liquid, such as a solvent or the like. This leads to the spontaneous vaporisation and to the desired atomisation of the non-vaporised liquid. The produced liquid droplets then form the desired aerosol.

In particular, when the liquid strikes the contact or deflecting surface there is a sudden, discontinuous formation of a vapour cushion between the hot surface and the actual jet. This leads to the successive atomisation, already mentioned above, of small amounts of the liquid and accordingly to substantially uniformly large liquid droplets.

The liquid jet may be employed as required for an unmetered or a metered atomisation and aerosol generation. The metering by means of the jet is used especially for the atomisation of medicament formulations, in particular for inhalation purposes. The solution according to the present proposal leads to an atomisation of a very defined proportion of the delivered liquid, so that the metering of the jet leads to an accurate metering of the atomised liquid and thus of the ejected medicament and active constituent.

The atomisation according to the present proposal in addition also leads to extremely reproducible properties, such as a narrow and constant droplet size distribution, uniform mean droplet diameter and/or narrow droplet velocity distribution, with in particular a low mean velocity of the aerosol. This is very advantageous when metering medicaments, active constituents or the like, since for example a defined proportion of droplets that reaches the lungs and that can be effectively absorbed can always be generated.

Further aspects, features, properties and advantages of the present invention are disclosed in the following description of preferred embodiments and with reference to the accompanying drawings, in which:

Fig. 1 is a diagrammatic view of a device according to the present application and in accordance with a first embodiment;

Fig. 2 is a diagrammatic view of a device according to the present application and in accordance with a second embodiment;

Fig. 3 is an enlarged view of the device according to Fig. 2;

Fig. 4 is a diagrammatic view of a device according to the present application and in accordance with a third embodiment;

Fig. 5 is a diagrammatic view of a device according to the present application and in accordance with a fourth embodiment; and

Fig. 6 is a diagrammatic view of a device in the form of an inhaler according to the present application and in accordance with a fifth embodiment.

In the figures the same reference numerals are used for identical or similar parts, even when the description is not repeated.

The schematic diagram according to Fig. 1 shows diagrammatically the construction of a device 1 according to the present application and in accordance with a first embodiment. The device 1 serves for the atomisation of a liquid 2, in particular a liquid medicament formulation in the sense mentioned in the introduction, a cosmetic agent, an industrial liquid, or the like.

The device 1 preferably comprises a nozzle 3 for generating a jet 4 of the liquid 2. In particular a free, i.e. non-laterally-directed jet 4, is formed.

The jet 4 preferably has an at least substantially circular cross-section with a diameter of in particular 1 to 50 µm, particularly preferably less than 20 µm or even less than 10 µm.

The jet 4 is ejected from the nozzle 3 preferably at a pressure of 0.05 to 3 MPa, in particular 0.1 to 0.3 MPa.

The device 1 furthermore comprises a hot or heatable contact surface 5 on which the jet 4 is incident.

The contact surface 5 may in principle have any suitable shape that is appropriate for the desired atomisation, and may thus for example be formed in a grid like manner or provided with openings. Preferably the contact

surface 5 forms an, in particular, continuous impact and deflecting surface for the jet 4.

The contact surface 5 can be warmed or heated by means of a heating device (not illustrated in Fig. 1), in order to vaporise partially the incident liquid 2 and thereby achieve the desired atomisation of the liquid 2. Preferably, only up to 15 Vol.%, in particular more than 1 or 2 Vol.% and/or less than 10 Vol.%, most preferably about 7 Vol.% or less, of the supplied liquid 2 is vaporised. The heating device preferably operates electrically. However, heating or input of thermal energy may also take place in any other convenient way, in particular by light or chemical processes, such as oxidation of a fuel by means of a catalyst.

The temperature of the contact surface 5 is preferably significantly above (e.g. by 20°C or 50°C) the boiling point of the liquid 2 or of an essential constituent of the liquid 2, such as a solvent. When water is used as solvent the temperature of the contact surface is preferably at least 120°C, in particular 150°C or more. Preferably, the starting temperature (temperature at the beginning just before the liquid 2 impinges on the contact surface 5) is kept at about 250°C or more, in particular up to 400°C. Thus, a spontaneous vaporisation without a delay in boiling can be achieved, i.e. a direct transition from the liquid to the gaseous state together with the desired increase in volume.

The temperature of the contact surface 5 is also preferably so high that no residues or at least no residues relevant for a medical application are formed on the contact surface 5, in particular as regards the optimised composition or formulation of the liquid 2 for such an application.

Another aspect is the dispensing ratio or liquid flow (volume of liquid before partial vaporization per time unit). Preferably, the liquid flow is 5 to 100 µl/s, in particular about 10 to 50 µl/s.

The contact surface 5 is preferably formed of metal, semiconductor material such as silicon, ceramics or glass. In particular the contact surface 5 is formed by the surface of a corresponding plate-shaped piece, side wall or a

corresponding coating. Alternatively or in addition the material and/or the contact surface 5 may be coated, for example with one of the aforementioned materials or with silicon nitride, silicon carbide, Teflon or other suitable materials, in particular to minimise or prevent formation of residues and/or dirt.

The thermal capacity of the body forming the contact surface 5 is preferably sufficiently large to maintain the surface temperature sufficiently constant during the atomisation process. The thermal capacity is however preferably chosen to be not too large, so that the heat loss of the heating device (not shown) associated with the contact surface 5 can be minimised or at least kept to acceptable limits. Alternatively or in addition the heating device (heater) responds sufficiently rapidly so that the temperature can be maintained at least in a desired range during the atomisation process.

In particular, the following equation is at least essentially fulfilled:

$$(0.001 \cdot T^{1.9} / (1 + 0.32 \cdot dV/dt) - 4.7 \cdot e^{-0.053(dV/dt+5)}) \cdot V =$$
$$1000 \bullet (m_H \cdot c_H \cdot \Delta T + E_{zu}) / (c_F \cdot (100 - T_R) + q_F + 0.4 \cdot (T - 100 - \Delta T/2))$$

with:

	T	temperature of heater at the beginning of dispensing, in °C;
	V	total volume of dispensed liquid per dose, in µl;
	dV/dt	liquid flow, in µl/s;
	m_H	mass of heater, in g;
	c_H	specific heat capacity of heater, in J/(g·K);
	ΔT	amount of temperature change of the heater during dispensing action, in K;
	E_{zu}	additional energy supply to the heater during dispensing action, in K;
	c_F	specific heat capacity of liquid, in J/(g·K);
	T_R	room or environment temperature
	q_F	specific heat of evaporation of liquid, in J/g.

Preferably, the total volume of liquid dispensed per dose or actuation of the dispensing device 1 is about 10 to 100 µl, in particular about 15 to 60 µl.

Particularly preferably the pressure with which the jet 4 impacts on the contact surface 5 can be adjusted, controlled or regulated. In particular this is achieved by adjusting, controlling or regulating the pressure at which the jet 4 exits from the nozzle 3. Alternatively or in addition, the distance between the nozzle 3 and contact surface 5 and/or the impact point on the contact surface 5 can to this end also be varied, for example by altering the direction of the jet or using another nozzle 3.

The distance of the nozzle 3 from the contact surface 5 – i.e. the free jet length – is preferably small and in particular is less than 1 mm. Preferably the distance is less than 500 µm and in particular is basically 100 to 300 µm. Thus, a relatively low feed pressure and/or exit pressure at the nozzle 3 is sufficient to allow the liquid 2 to strike the contact surface 5 still with a relatively high or at least sufficient pressure of preferably 0.05 to 3 MPa, in particular 0.1 to 0.3 MPa.

When the liquid 2 or the jet 4 strikes the contact surface 5 only a very small proportion of the liquid 2 is spontaneously vaporised. In particular a vapour cushion is intermittently formed between the contact surface 5 and the actual jet 4 and the non-vaporised liquid 2. The increase in volume during the transition from the liquid to the gaseous phase leads to the desired atomisation of liquid 2 into very small, substantially uniformly large droplets 6 that form an aerosol 7 together with the ambient atmosphere, in particular air.

The contact surface 5 is preferably formed substantially microscopically smooth, at least in its impact region. The contact surface 5 may if necessary be structured macroscopically and/or microscopically – i.e. provided with protuberances and/or depressions – or formed smooth, in order to influence the aerosol formation in a desired way. In particular a microstructuring of the contact surface 5 can improve the efficiency of the atomisation, in that the vaporisation of liquid 2 takes place in open microcavities. Due to the microcavities the vaporised liquid and the energy thereby ejected can be focused on or directed at the following liquid 2 in the jet. Alternatively or in addition the contact surface 5 may also be formed micro-rough. Different reflection properties are thereby produced. This is conducive to a broad spatial

distribution and angular distribution of the velocities of the resultant droplets 6, and thus produces a "diffuse scattering".

Preferably the droplets 6 have a narrow and uniform size distribution. In particular a constant impact velocity of the liquid 2 on the contact surface 5 is conducive to a uniform size distribution, since each liquid element is thereby subjected to uniform dynamical and thermal influences, which is conducive to the desired uniformity of the droplet size.

In order however to assist a specific spatial localisation of the droplets 6 and the formation of a defined aerosol cloud, the contact and deflecting surface 5 preferably has a concave, for example parabolic, shape. In addition or alternatively guidance devices (not shown) for the aerosol 7 or means to produce swirling or deflection of the aerosol 7 or the like may be provided.

The droplets 6 formed in the atomisation preferably have no substantially uniform velocity direction, but in particular exhibit a broad spatial distribution of the directions and angular distribution of their velocities. This broad spatial velocity distribution is assisted by the preferred deflection and the preferred reflection of the liquid 2 at the contact and deflecting surface 5.

In addition the deflection and/or the reflection of the liquid 2 at the contact and deflecting surface 5, as well as preferably the diffused spatial distribution of the movement directions of the droplets 6, are conducive to the formation of a quasi-stationary aerosol cloud or at least to a substantial decrease in the propagation velocity of the aerosol 7 and the velocities of the droplets 6, in particular to less than 1 m/sec immediately after the contact surface 5.

The impact angle of the jet 4 on the contact surface 5, i.e. the angle between the jet 4 and the contact surface 5, is preferably between 10° and 90°, in particular between 40° and 70°.

The droplets 6 preferably have a mean diameter of less than 10 µm, in particular of 1 to 7 µm, most particularly preferably of substantially 5 µm or less, in order to achieve a high pulmonary accessibility during inhalation.

The mean volume of the droplets 6 is preferably less than 1 pl, in particular substantially 0.1 pl or less.

The volume flow of atomised liquid 2 is preferably at least 30 µl/sec. Thus, the amount of aerosol 7 appropriate for an inhalation can be generated with a sufficient amount of an active constituent in a sufficiently short time of for example only one second or a few seconds.

A metering of the jet 4 preferably takes place. Thus, the aerosol 7 and thereby the ejected amount of medicament formulation or the like can be metered in a simple and effective manner.

The generation of the aerosol 7 is preferably followed by inhalation by a user (not shown). The device 1 is accordingly preferably designed as an inhaler or for medical aerosol treatment.

However, the aerosol 7 – in particular depending on the liquid 2 that is used – may also be employed for other purposes, in particular for cosmetic or technical purposes. This has already been discussed in the introduction.

Further embodiments according to the present invention are described hereinafter with the aid of the further figures, the respective description concentrating on essential differences compared to the other embodiments. Descriptions and explanations regarding the other embodiments and in the introductory part thus apply as appropriate or suitably amplified.

Fig. 2 shows in the form of a very schematic diagram a second embodiment of the device 1 according to the present proposal. Fig. 3 shows the device 1 on an enlarged scale. In contrast to the first embodiment the nozzle 3 and the contact surface 5 are in this case formed as a block or as one piece, in particular as a monobloc. A compact, universally usable structural part is obtained, which due to the preferred very small distance between the contact surface 5 and the nozzle 3 – as already discussed on the basis of the first embodiment – operates satisfactorily with very low liquid pressures of in particular less than 3 MPa.

In addition the device 1 according to the second embodiment comprises a plurality of nozzles 3 that generate preferably at least substantially parallel – not shown in Fig. 3 – jets 4 of the liquid 2, which in particular impact at different regions on the preferably common contact surface 5. The nozzles 3 are in this embodiment preferably provided via separate feed lines 8 with the liquid 2 (not shown in Fig. 3).

Fig. 3 furthermore shows a heating device 9 with electrical connections 10 that is associated with the contact surface 5. The heating device 9 is electrically operated and forms, possibly directly or with an appropriate coating, protective layer or the like, the contact surface 5.

Fig. 4 shows in a perspective view a third embodiment of the device 1 according to the proposal with only one nozzle 3. The nozzle 3 and the contact and deflecting surface 5 are in this case too formed as a common – preferably multipart – structural part corresponding to the second embodiment.

The feed line 8 for the liquid 2 to the nozzle 3 has a plurality of parallel channels 11 that serve to filter the liquid 2 in order to prevent a blockage of the very fine nozzle 3. The channels 11 thus form a filter device. The channels 11 are connected in parallel to a subsidiary, common collecting region 12 that feeds the liquid 2 to the nozzle 3.

The channels 11, the collecting region 12 and/or the nozzle 3 are preferably formed by corresponding depressions in a surface of an in particular plate-shaped material piece 13, for example by etching, laser abrasion, stamping, injection moulding or the like, and are covered in particular by a cover 14, which has been partly cut away in Fig. 4 for the sake of clarity.

The nozzle 3 in the illustrated example opens onto a side wall of a preferably groove-shaped recess 15. The oppositely-facing wall forms the contact and deflecting surface 5 and carries the heating device 9. In the illustrated example the oppositely-facing wall is formed from the material piece 13 and the cover 14. However, other structural solutions are also possible in this case.

Fig. 5 shows in a diagrammatic, perspective representation a fourth embodiment of the device 1 according to the proposal. The fourth embodiment resembles the third embodiment. Instead of one nozzle 3, in this case a plurality of nozzles 3 are provided, which are preferably connected in parallel to the common collecting region 12. Correspondingly, in the fourth embodiment a plurality of jets 4 of the liquid 2 (shown only by dotted lines in Fig. 5) can be generated, which preferably strike different regions of the contact surface 5 and can be atomised in parallel in the desired manner to produce a common aerosol 7. This permits the atomisation of a large amount of liquid 2 in a short time, in particular at a rate of at least 30 µl/sec.

According to a variant (not illustrated) the jets 4 and individual groups of jets 4 strike different contact and deflecting surfaces 5. If necessary the various surfaces 5 may then vary as regards their properties, in particular distance to the respective nozzle 3, inclination, surface state, or the like.

The ejection of the liquid 2 to be atomised, in parallel and simultaneously through a plurality of nozzles 3, enables a large amount of liquid 2 to be atomised in a short time, whereby, as already explained, a relatively large amount of aerosol 7 with a small mean droplet size can be formed. This parallel and simultaneous ejection through a plurality of nozzles 3 may also be employed independently of the described embodiments and also independently of the proposed solution and atomisation discussed here. Particularly preferably the parallel ejection through a plurality of nozzles 3 may also be employed in another type of atomiser, in particular the nebuliser obtainable under the trade name "Respimat", or in an atomiser as disclosed in particular in WO 91/14468 A1, WO 97/12687 A1 or WO 2005/080001 A1, wherein for example several pairs of jets of the liquid 2 to be atomised are generated by several nozzles 3 and the jets intersect in pairs for the atomisation into small droplets.

The second, third and fourth embodiments of the device 1 according to the proposal may be manufactured in particular on a miniaturised scale.

The device 1 according to the third and fourth embodiments is in particular produced by forming or recessing the nozzle(s) 3 and the feed line(s) 8 by

etching in the material piece 13 on the side subsequently covered by the cover 14.

The material piece 13 preferably consists of silicon. In particular the piece is a silicon wafer or some other plate piece for a plurality of material pieces 13. The techniques known from semiconductor technology, such as lithography, covering with a photolacquer or the like, may therefore be used to form the structures.

The production of the structures, such as the nozzle 3, the feed line 8 and the like, preferably takes place in the wafer or in another plate piece before the subdivision or the cutting up into the individual material pieces 13, i.e. in parallel and simultaneously for a plurality of devices 1.

The structured wafer or the other plate piece is then covered over the whole surface with the cover 14. The cover 14 preferably consists of glass or silicon, and is possibly also a silicon wafer or the like. The cover 14 is securely joined, preferably by anodic bonding or another suitable method, to the wafer or plate piece forming the material pieces 13, to produce a plate composite.

The thickness of the lower layer and/or of the material piece 13 and/or of the cover 14 is preferably in each case 200 to 800 µm, in particular substantially about 500 µm.

Before forming the recess 15 – possibly also before the connection to the material pieces 13 – the cover 14 is preferably provided on the flat side of the cover 14 facing away from the material pieces 13, with a conducting structure for the subsequent formation of the electrical connections 10, in particular by coating certain regions, partial removal of a corresponding, electrically conducting coating, or the like.

The recesses 15 of the devices 1 in the plate composite are then formed preferably in a thickness of about 100 to 300 µm, in particular by suitably cutting into the plate composite with a suitable saw blade. The production of the recesses 15 may however be accomplished in another suitable way, for

example by laser abrasion, etching or the like. The nozzles 3 are formed and opened by the production of the recess(es) 15.

After the production of the recess(es) 15 – and preferably before the separation of the plate composite into individual devices 1 – the heating devices 9 are formed in particular by vapour deposition of an electrically conducting material or by another coating method on the side wall(s) of the recess(es) 15 lying opposite the nozzle 3 and formation of a suitable conductor arrangement or guidance. An electrical connection to the connections 10 is produced at the same time. The exact structure of the heating devices 9 is not shown in figs 4 and 5, since the heating devices 9 are preferably covered by a coating, protective layer or the like, not identified in more detail, consisting in particular of silicon nitride, silicon carbide, Teflon or another suitable material, that forms the contact surface 5.

Finally, the plate composite is separated into the individual devices 1, in particular by sawing or some other cutting or separation method.

The preferred sequence of steps explained hereinbefore permits a very simple and inexpensive production of the device 1 having defined properties and low tolerances.

The device 1 produced according to the proposal constitutes a common – optionally block-like and/or one-piece or integrated – structural part for the feed line(s) 8, the nozzle(s) 3, the contacts surface(s) 5 and possibly the heating device(s) 9. This arrangement allows a simple and rapid installation of the device 1, in particular where the desired relationships of the nozzle 3 to the contact surface 5, especially a specific interspacing, have already been fixed by the device 1 according to the proposal.

Fig. 6 shows in a schematic, section-like view a device 1 in the form of an inhaler according to a fifth embodiment of the present invention.

The liquid 2 is stored in a container 16 and can be ejected through nozzle 3 as a jet 4 onto the heated contact surfaces 5 to partially vaporise the liquid 2 and

form the aerosol 7 as explained above in connection with the other embodiments. The aerosol 7 is discharged via an optional mouthpiece 17.

The device 1 / inhaler comprises preferably a supply means or pump 18. In the present case, the pump 18 comprises a supply tube 19, which is preferably connected with container 16 and extends into container 16 and into the liquid 2. The supply tube 19 extends with its other end into a pump chamber 20 and acts as a pump piston. A check valve 21 is preferably provided at the end of the supply tube 19 extending into the pump chamber 20.

The device 1 or pump 18 further comprises a preferably manually operated actuator 22. Preferably, the actuator 22 can be pivoted and acts with a curve 23 on a counter element 24 associated to the pump 18, container 16, and/or supply tube 19 directly or indirectly.

When the actuator 22 is operated, in particular pressed or pivoted inwardly form the position shown in Fig. 6, the supply tube 19 and preferably the container 16 are moved downwardly from the position shown in Fig. 6. During this suction stroke, valve 21 is open and fluid 2 is drawn from the container 16 through the supply tube 19 into the pump chamber 20. Simultaneously, a spring 25 is biased that is directly or indirectly associated to the container 16 and/or supply tube 19.

At the end of the suction stroke, the biased spring 25 may be blocked in its biased or compressed position or may be released directly. If the spring 25 is blocked in its biased position, it may be released after release of the actuator 22 and/or after actuating any other release mechanism or the like.

With or after release, the force of the spring 25 is used to quickly return the supply tube 19 – in Fig. 6 in upward direction – into the pump chamber 20, so that the valve 21 closes and a high fluid pressure is generated in the pump chamber 20 during the compression or pump stroke. Thus, the liquid 2 is ejected from the pump chamber 20 through nozzle 3 as jet 4 onto contact surface 5 as schematically shown in Fig. 6.

In the present embodiment, the contact surface 5 is formed preferably by an edge of a flat or plate-shaped a member 26. The member 26 is heated by at least one associated heating element 27 of the heating device 9, in particular sandwiched between two heating elements 27. The inhaler / heating device 9 preferably comprises a battery or accumulator 28, in particular a lithium ion accumulator or the like, for providing the necessary energy for powering the electrically operated heating elements 27.

Preferably the heating device 9 additionally comprises a controller 29 and/or a display 30 e.g. a lamp or the like. Controller 29 controls the electric power supplied to the at least one heating elements 27 and may preferably control the temperature preferably of the member 26 / contact surface 5.

The display 30 preferably indicates when the contact surface 5 has reached its temperature, the starting temperature T mentioned above, such as 250 to 400°C, so that the desired partial vaporisation can take place when the jet 4 is directed onto the contact surface 5.

The heating device 9 may be switched on and/or off depending on the actuation of the pump 18. Vice versa, the pump 18 may be actuated and/or the spring 25 may be released from its biased position preferably only when the contact surface 5 has reached the desired / required temperature for generating the aerosol 7 in the desired manner as described above.

The battery / accumulator 28 may be exchanged and/or reloaded. For example, the device 1 / inhaler may be inserted into and/or connected to – preferably wireless and/or inductively – to a charging device (not shown).

Preferably, the device 1 / inhaler meters and dispenses the liquid 2 in defined doses (each pump stroke corresponds to one stroke), preferably with about 10 to 100 µl as mentioned above. Preferably, the liquid is dispensed with a liquid flow of 5 to 100 µl/s, in particular about 10 to 50 µl/s.

Alternatively or additionally, the above equation and/or other data and measures apply for the inhaler at least substantially.

The features of the different embodiments and the different embodiments can be combined any suitable manner and/or combined or used in other dispensers, inhalers or the like.

Preferably the liquid 2 is, as already mentioned, a medicament formulation, for example an aqueous or ethanolic medicament formulation. It may however also involve another type of medicament formulation, a suspension or the like.

Preferred constituents and/or formulations of the preferably medicinal liquid 2 are listed hereinafter. As already mentioned, these may be aqueous or non-aqueous solutions, mixtures of ethanolic or solvent-free formulations or the like. Mixtures may contain in particular two or more, preferably three or four, medicaments, most preferably in ethanolic formulations. The liquid 2 particularly preferably contains the following:

All inhalable compounds, for example also inhalable macromolecules, as disclosed in EP 1 003 478, are used as pharmaceutically active substances, substance formulations or substance mixtures. Preferably substances, substance formulations or substance mixtures that are used for inhalation purposes are employed to treat respiratory pathway conditions.

Particularly preferred in this context are medicaments that are selected from the group consisting of anticholinergic agents, betamimetics, steroids, phosphodiesterase IV inhibitors, LTD4 antagonists and EGFR kinase inhibitors, antiallergic agents, ergot alkaloid derivatives, triptanes, CGRP antagonists, phosphodiesterase V inhibitors, as well as combinations of such active substances, e.g. betamimetics plus anticholinergic agents or betamimetics plus antiallergic agents. In the case of combinations at least one of the active constituents contains preferably chemically bound water. Anticholinergic agent-containing active substances are preferably used, as single preparations or in the form of combination preparations.

The following in particular may be mentioned as examples of effective constituents or their salts:

Anticholinergics which may be used are preferably selected from among tiotropium bromide, oxitropium bromide, flutropium bromide, ipratropium bromide, glycopyrronium salts, trospium chloride, tolterodine, tropenol 2,2-diphenylpropionate methobromide, scopine 2,2-diphenylpropionate methobromide, scopine 2-fluoro-2,2-diphenylacetate methobromide, tropenol 2-fluoro-2,2-diphenylacetate methobromide, tropenol 3,3',4,4'-tetrafluorobenzilate methobromide, scopine 3,3',4,4'-tetrafluorobenzilate methobromide, tropenol 4,4'-difluorobenzilate methobromide, scopine 4,4'-difluorobenzilate methobromide, tropenol 3,3'-difluorobenzilate methobromide, scopine 3,3'-difluorobenzilate methobromide, tropenol 9-hydroxy-fluorene-9-carboxylate methobromide, tropenol 9-fluoro-fluorene-9-carboxylate methobromide, scopine 9-hydroxy-fluorene-9-carboxylate methobromide, scopine 9-fluoro-fluorene-9-carboxylate methobromide, tropenol 9-methyl-fluorene-9-carboxylate methobromide, scopine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine benzilate methobromide, cyclopropyltropine 2,2-diphenylpropionate methobromide, cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide, cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide, tropenol 9-hydroxy-xanthene-9-carboxylate methobromide, scopine 9-hydroxy-xanthene-9-carboxylate methobromide, tropenol 9-methyl-xanthene-9-carboxylate methobromide, scopine 9-methyl-xanthene-9-carboxylate methobromide, tropenol 9-ethyl-xanthene-9-carboxylate methobromide, tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide and scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the solvates and/or hydrates thereof.

Betamimetics which may be used are preferably selected from among albuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, indacaterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmeterol, salmefamol, soterenot, sulphonterol, tiaramide, terbutaline, tolubuterol, CHF-1035,

HOKU-81, KUL-1248, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzolsulphonamide, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1*H*-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1.4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1.4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1.4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1.2.4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1.4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluormethylphenyl)-2-tert.-butylamino)ethanol and 1-(4-ethoxycarbonyl-amino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

Steroids which may be used are preferably selected from among prednisolone, prednisone, butixocortpropionate, RPR-106541, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, ST-126, dexamethasone, (S)-fluoromethyl 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothionate, (S)-(2-oxo-tetrahydro-furan-3S-yl) 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothionate and etiprednol-dichloroacetate (BNP-166), optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

PDE IV-inhibitors which may be used are preferably selected from among enprofyllin, theophyllin, roflumilast, ariflo (cilomilast), CP-325,366, BY343, D-4396 (Sch-351591), AWD-12-281 (GW-842470), N-(3,5-dichloro-1-oxo-

pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide, NCS-613, pumafentine, (-)p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[s][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide, (R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone, 3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropyl-methoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], (R)-(+)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate, (S)-(-)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate, CDP840, Bay-198004, D-4418, PD-168787, T-440, T-2585, arofyllin, atizoram, V-11294A, Cl-1018, CDC-801, CDC-3052, D-22888, YM-58997, Z-15370, 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(*tert*-butyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridin, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

LTD4-antagonists which may be used are preferably selected from among montelukast, 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid, 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane-acetic acid, pranlukast, zafirlukast, [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707 and L-733321, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof.

EGFR-kinase inhibitors which may be used are preferably selected from among cetuximab, trastuzumab, ABX-EGF, Mab ICR-62, 4-[(3-chloro-4-

fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-

yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)-amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-

(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

By acid addition salts, salts with pharmacologically acceptable acids which the compounds may possibly be capable of forming are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

Examples of antiallergics are: disodium cromoglycate, nedocromil.

Examples of derivatives of the ergot alkaloids are: dihydroergotamine, ergotamine.

For inhalation it is possible to use medicaments, pharmaceutical formulations and mixtures including the abovementioned active constituents, as well as their salts, esters and combinations of these active constituents, salts and esters.

Claims:

1. Method for the atomisation of a liquid (2), in which the liquid (2) is directed as a jet (4) onto a hot or heated contact surface (5) and, thus, partially vaporised in order to atomise the liquid (2) in a non-directed manner into small droplets (6) and generate an aerosol (7).

2. Method according to claim 1, characterised in that small amounts of the liquid (2) are atomised in succession and/or in parallel.

3. Method according to claim 2, characterised in that each individual amount is atomised into a plurality of droplets (6).

4. Method according to one of the preceding claims, characterised in that the liquid (2) is atomised into droplets (6) without employing side walls.

5. Method according to one of the preceding claims, characterised in that the volume flow of the atomised liquid (2) is at least 30 µl/sec.

6. Method according to one of the preceding claims, characterised in that the liquid (2) is delivered during the atomisation continuously and/or only in the form of the preferably defined or focused jet (4) and/or as a free jet (4) onto the contact surface (5).

7. Method according to one of the preceding claims, characterised in that the jet diameter is adjusted, controlled or regulated in order to achieve a desired droplet size and/or propagation velocity of the aerosol (7) and/or that the jet diameter is less than 1 to 50 µm, in particular less than 20 µm.

8. Method according to one of the preceding claims, characterised in that the aerosol (7) is metered by metering the jet (4).

9. Method according to one of the preceding claims, characterised in that the liquid flow or jet flow is about 5 to 100 µl/s and/or that the liquid (2) is dispensed in metered doses of preferably about 10 to 100 µl.

10. Method according to one of claims 6 to 9, characterised in that the free jet length is less that 1 mm, in particular less than 500 µm, particularly preferably substantially 100 to 300 µm.

11. Method according to one of the preceding claims, characterised in that the liquid (2) is delivered for the atomisation simultaneously in a plurality of jets (4)., preferably wherein the jets (4) impact on various contact surfaces (5) or various regions of the same contact surface (5).

12. Method according to one of the preceding claims, characterised in that the liquid (2) is deflected on the contact surface (5), especially a deflecting surface, and in particular a part of the liquid (2) is vaporised directly without boiling delay on impact on the deflecting surface (5).

13. Method according to one of the proceeding claims, characterised in that the temperature of the contact surface (5) is adjusted, controlled or regulated in order to achieve a desired droplet size and/or propagation velocity of the aerosol (7).

14. Method according to one of the proceeding claims, characterised in that the temperature of the contact surface (5) is preferably at least 20°C, most particularly preferably at least 50°C, above the boiling point of the liquid (2) or at least of a constituent of the liquid (2), such as a solvent, and/or that the temperature of the contact surface (5) is about 250 to 400°C at least at the beginning of vaporization or dispensing of liquid (2).

15. Method according one of the proceeding claims, characterised in that the contact surface (5) is electrically heated and/or heated by light radiation and/or chemically heated.

16. Method according to one of the proceeding claims, characterised in that the liquid (2) impacts at an angle of 10° to 90°, preferably 40° to 70°, on the contact surface (5).

17. Method according to one of the proceeding claims, characterised in that the impact angle of the liquid (2) on the contact surface (5) is adjusted, controlled or regulated in order to achieve a desired droplet size and/or propagation velocity of the aerosol (7).

18. Method according to one of the proceeding claims, characterised in that the liquid (2) is delivered at, or strikes the contact surface (5) at a pressure of 0.05 to 3 MPa, preferably 0.1 to 0.3 MPa.

19. Method according to one of the proceeding claims, characterised in that the delivery pressure of the liquid (2) is adjusted, controlled or regulated in order to achieve a desired droplet size and/or propagation velocity of the aerosol (7).

20. Method according to one of the proceeding claims, characterised in that the aerosol (7) is generated only by partial vaporisation and/or that the liquid (2) is directed only as preferably focused or defined jet (4) of liquid (2) onto the contact surface (5).

21. Method according to one of the proceeding claims, characterised in that only up to 15 Vol.% of the liquid (2) is vaporised when impinging onto the contact surface (5).

22. Method according to one of the preceding claims, characterised in that the propagation velocity of the aerosol (7) is very low, in particular less than 1 m/sec.

23. Method according to one of the preceding claims, characterised in that the mean diameter of the droplets (6) is less than 10 μm, preferably 1 to 7 μm, in particular substantially 5 μm or less and/or that the mean volume of the droplets (6) is less than 1 pl, in particular substantially 0.1 pl or less.

24. Method according to one of the preceding claims, characterised in that a medicament formulation or a cosmetic agent is used as liquid (2) and atomised.

25. Device (1) for atomising liquid (2), in particular for carrying out a method according to one of the preceding claims, with a nozzle (3) for generating a preferably free jet (4) of the liquid (2) and with a contact surface (5) on which the jet (4) impacts,

characterised in

that the contact surface (5) can be heated so that a part of the liquid (2) is vaporised on impact with the contact surface (5), in order to generate an aerosol (7).

26. Device according to claim 25, characterised in that the liquid (2) is free of gas.

27. Device according to claim 25 or 26, characterised in that the liquid (2) is a liquid medicament formulation or a cosmetic agent.

28. Device according to one of claims 25 to 27, characterised in that the jet (4) can be ejected from the nozzle (3) or impacts on the contact surface (5) at a pressure of 0.05 to 3 MPa, preferably 0.1 to 0.3 MPa.

29. Device according to one of claims 25 to 28, characterised in that the jet (4) has a substantially round cross-section, and/or that the mean diameter of the jet (4) is 1 to 50 µm, in particular less than 20 µm, on exiting from the nozzle (3) or when striking the contact surface (5), and/or that the free jet length is less than 1 mm, in particular less than 500 µm, particularly preferably substantially 100 to 300 µm

30. Device according to one of claims 25 to 29, characterised in that that the liquid flow or jet flow is about 5 to 100 µl/s and/or that the liquid (2) is dispensed in metered doses of preferably about 10 to 100 µl.

31. Device according to one of claims 25 to 30, characterised in that only up to 15 Vol.% of the liquid (2) is vaporised when impacting onto the contact surface (5).

32. Device according to one of claims 25 to 31, characterised in that a plurality of jets (4) can optionally be produced by means of a plurality of nozzles (3), in which the jets (4) impact on various contact surfaces (5) or various regions of the same contact surface (5).

33. Device according to one of claims 25 to 32, characterised in that the contact surface (5) is at a distance of at most 15 mm, in particular less than 5 mm, and most particularly preferably less than 1 mm, from the nozzle (3).

34. Device according to one of claims 25 to 33, characterised in that the nozzle (3) and the contact surface (5) are rigidly joined to one another, preferably in the form of a block or a single piece, in particular as a monobloc or common structural part.

35. Device according to one of claims 25 to 34, characterised in that the temperature of the contact surface (5) can be adjusted, controlled or regulated.

36. Device according to one of claims 25 to 35, characterised in that the temperature of the contact surface (5) is preferably at least 20°C, most particularly preferably at least 50°C, above the boiling point of the liquid (2) or at least of a constituent of the liquid (2), such as a solvent, and/or that the temperature of the contact surface (5) is about 250 to 400°C at least at the beginning of vaporization or dispensing of liquid (2).

37. Device according to one of claims 25 to 36, characterised in that the contact surface (5) consists of metal, semiconductor material such as silicon, ceramics or glass, or is coated therewith or with silicon nitride, silicon carbide or Teflon.

38. Device according to one of claims 25 to 37, characterised in that the contact surface (5) is formed as a deflecting surface.

39. Device according to one of claims 25 to 39, characterised in that the contact surface (5) is microscopically smooth or is microstructured or is micro-rough.

40. Device according to one of claims 25 to 39, characterised in that the contact surface (5) is concave.

41. Device according to one of claims 25 to 40. characterised in that the impact angle of the jet (4) on the contact surface (5) is 10° to 90°, preferably 40° to 70°.

42. Device according to one of claims 25 to 41, characterised in that the impact angle of the jet (4) on the contact surface (5) can be adjusted, controlled or regulated.

43. Device according to one of claims 25 to 42, characterised in that the device (1) has a preferably electrically operated heating device (9) for heating or warming the contact surface (5).

44. Device according to one of claims 25 to 43, characterised in that the aerosol (7) forms an at least substantially stationary cloud and/or has an only very low propagation velocity, preferably less than 1 m/sec.

45. Device according to one of claims 25 to 44, characterised in that the aerosol (7) has a mean droplet size of less than 10 µm, preferably 1 to 7 µm, in particular substantially 5 µm or less.

46. Device according to one of claims 25 to 45, characterised in that the device (1) is designed for medical aerosol therapy and/or as an inhaler.

47. Method for the production of a device (1) according to one of claims 25 to 46, wherein the nozzle (3) is formed from a material piece (13) and a cover (14).

48. Method according to claim 47, characterised in that the nozzle (3) and optionally a feed line (8) to the nozzle (3) for the liquid (2) are formed by etching in the material piece (13) on the side facing towards the cover (14).

49. Method according to claim 47 or 48, characterised in that the cover (14) is rigidly joined to the material piece (13), in particular by anodic bonding.

50. Method according to one of claims 47 to 49, characterised in that the material piece (13) consists of silicon.

51. Method according to one of claims 47 to 50, characterised in that the cover (14) consists of silicon or glass.

52. Method according to one of claims 47 to 51, characterised in that the material piece (13) and the cover (14) are fabricated from plate-shaped material, wherein a plate composite is formed therefrom that is separated into a plurality of devices (1).

53. Method according to claim 52, characterised in that a recess (15) is formed between the nozzle (3) and the contact surface (5) by suitably cutting into the plate composite, in particular before the separation into individual devices (1).

54. Method according to one of claims 47 to 53, characterised in that a heating device (9) associated with the contact surface (5) is formed by vapour deposition on a side wall and is preferably covered by means of a protective layer to form the contact surface (5).

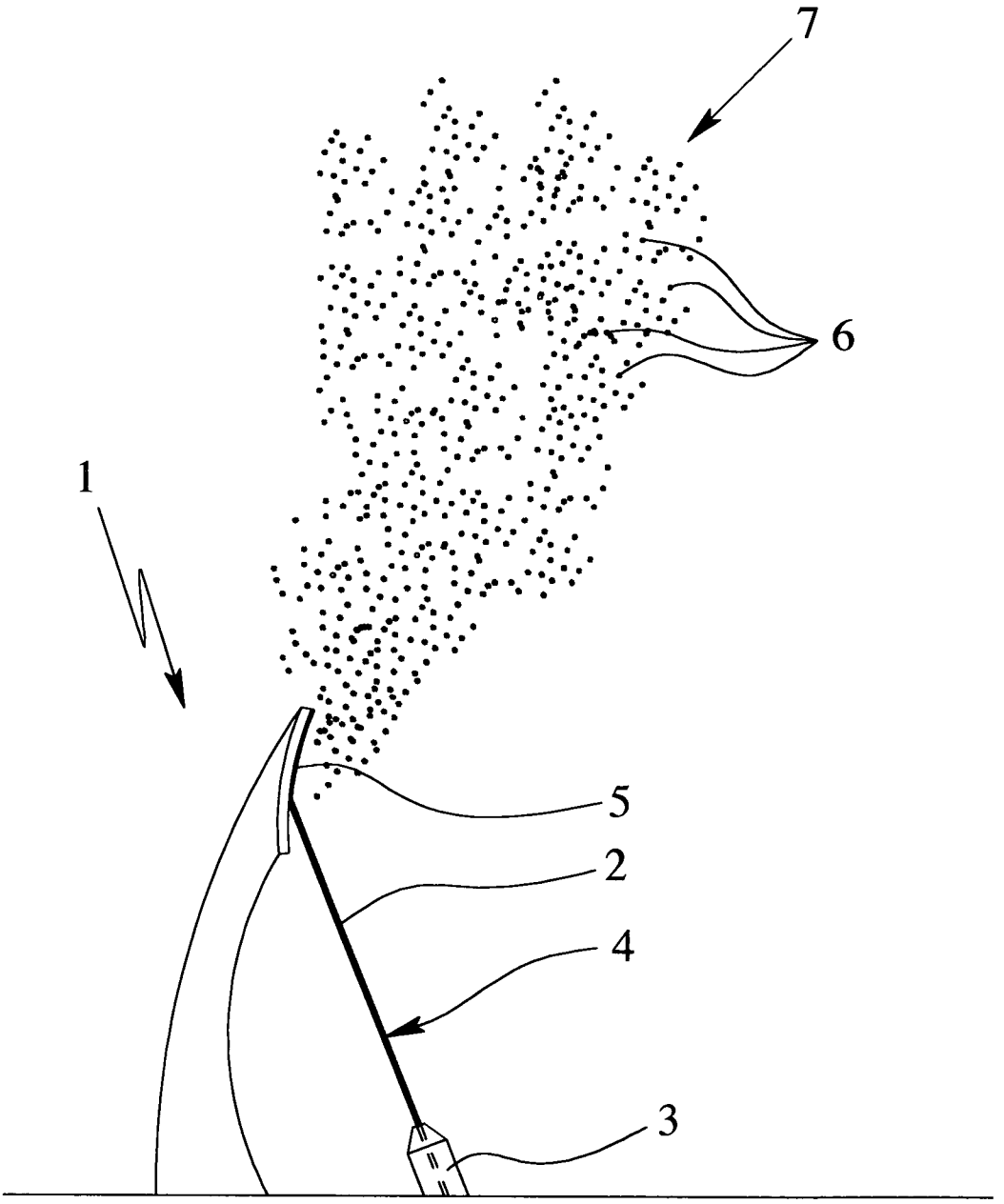


Fig. 1

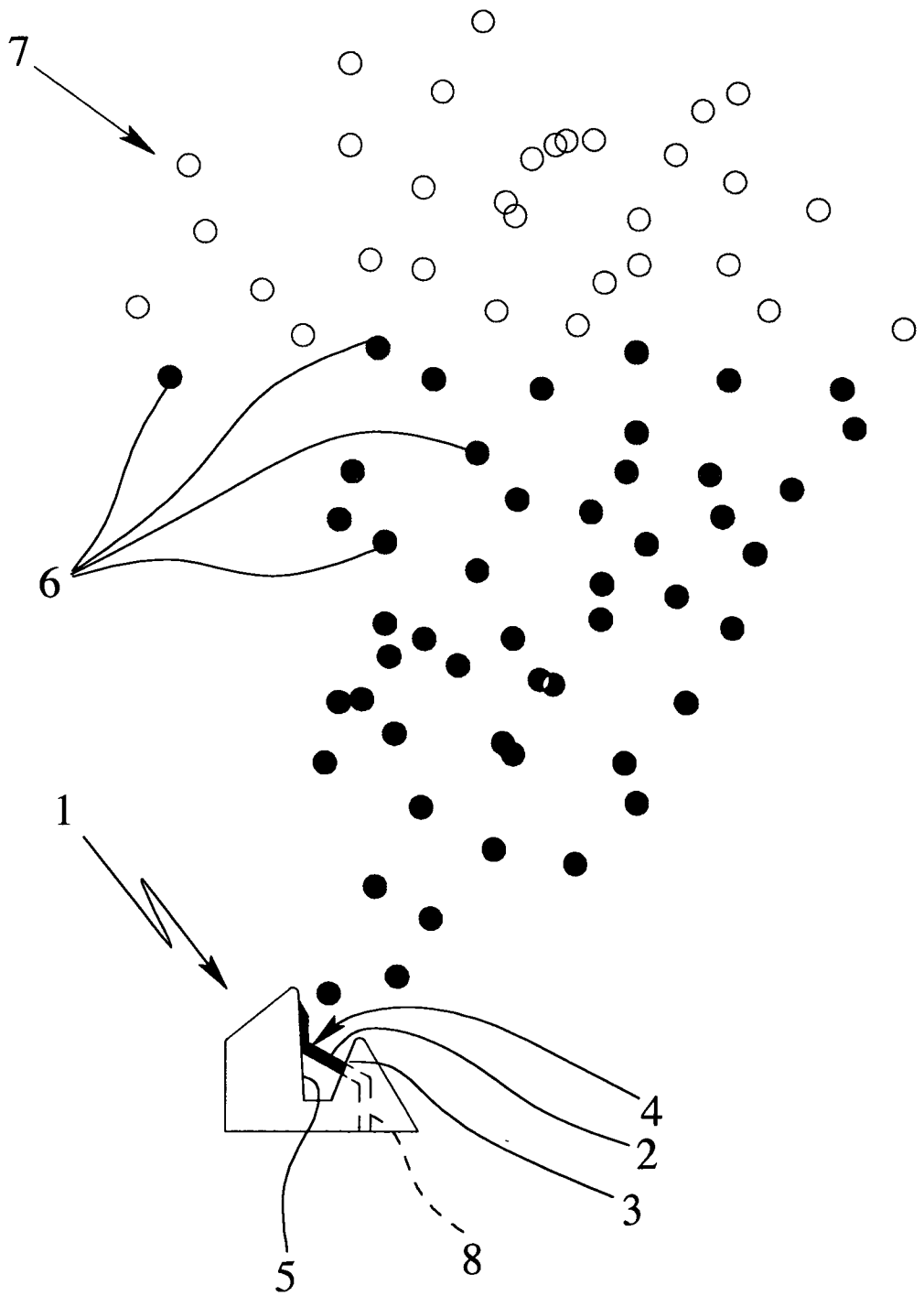


Fig. 2

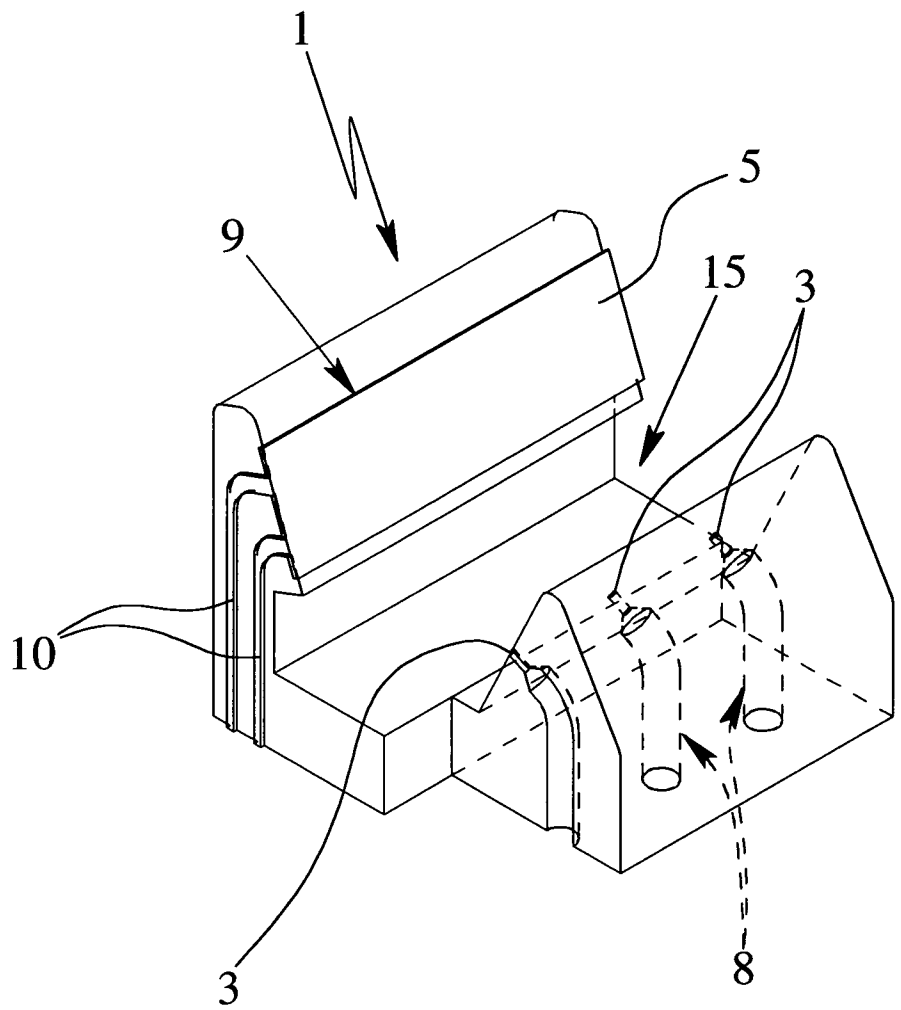


Fig. 3

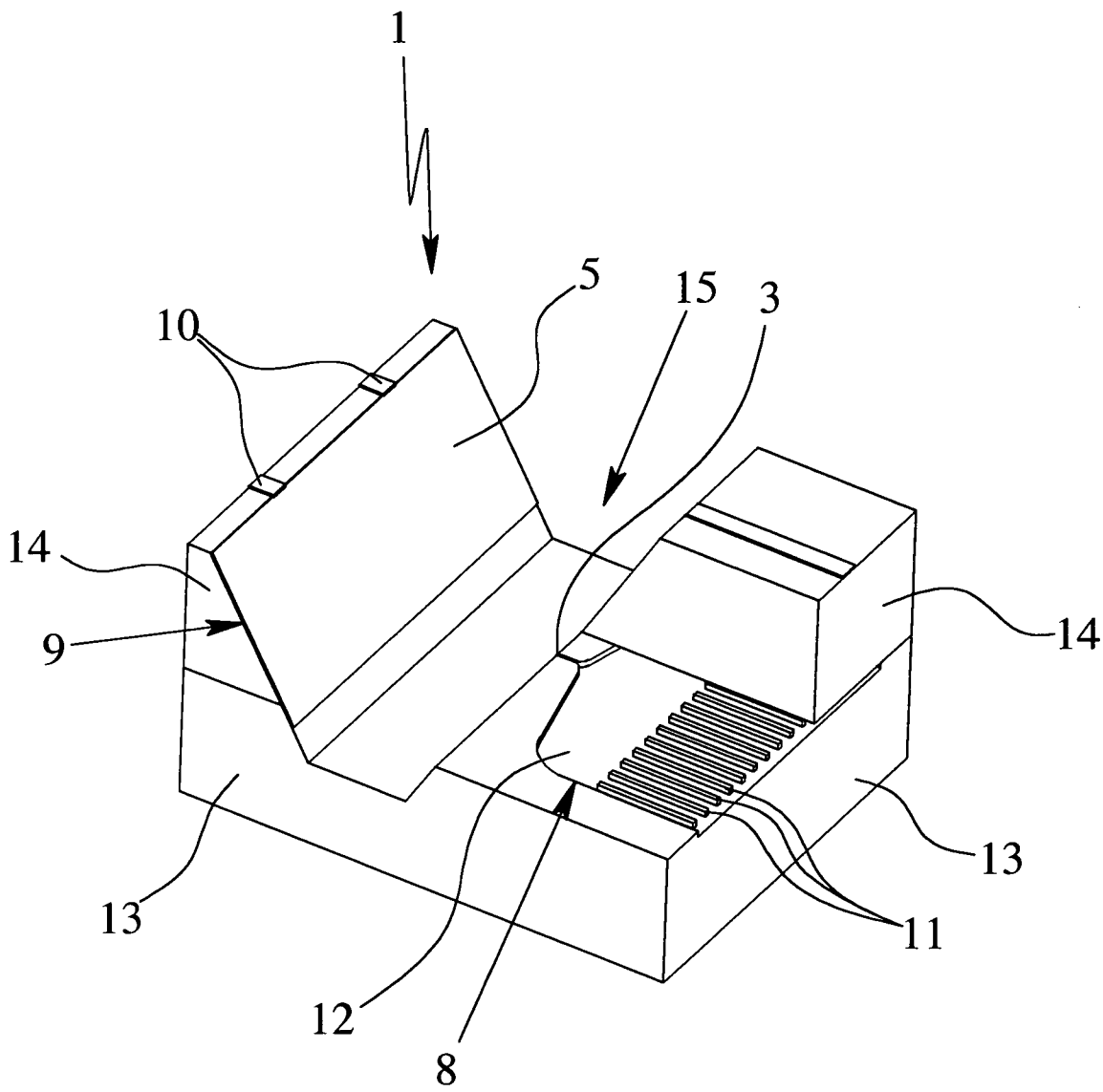


Fig. 4

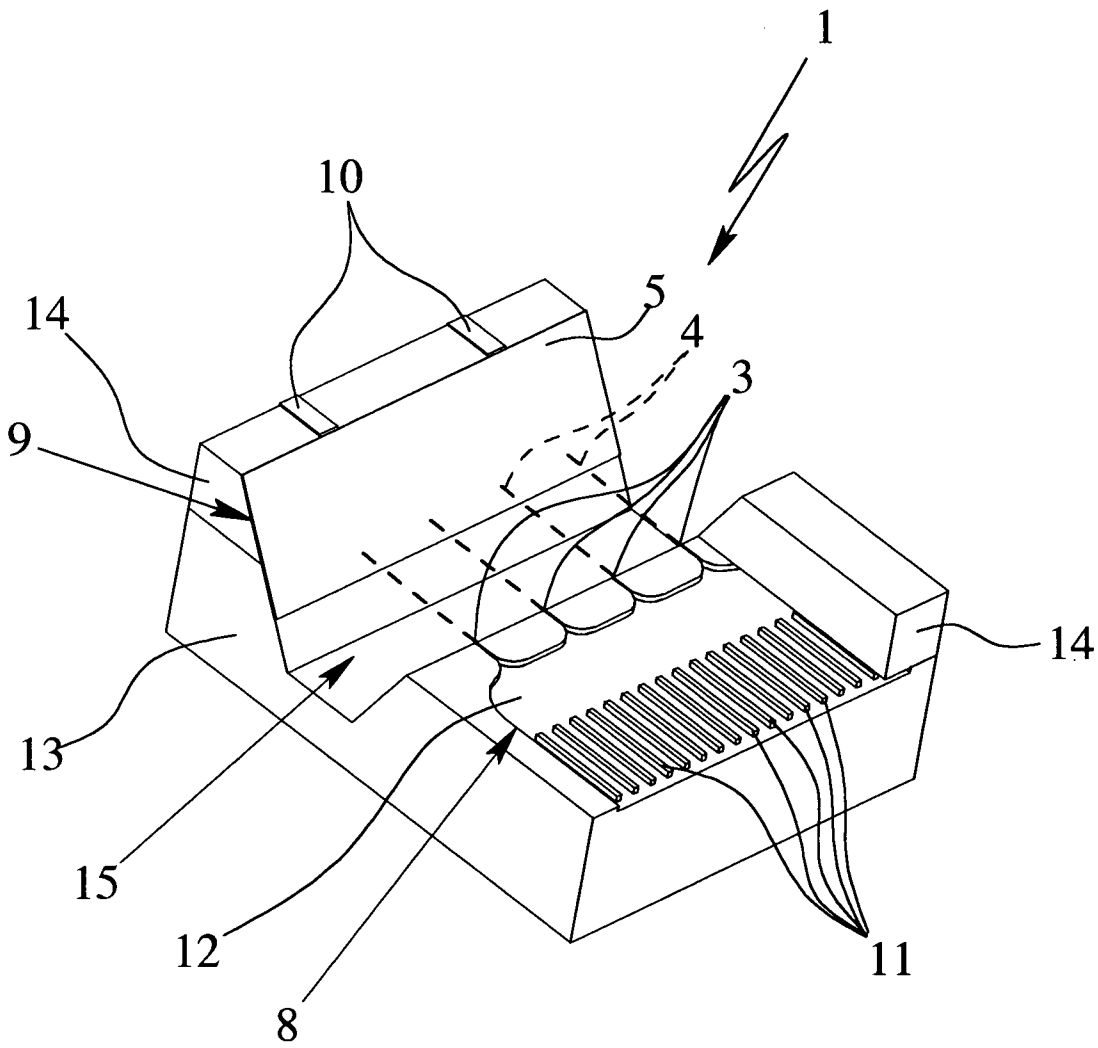


Fig. 5

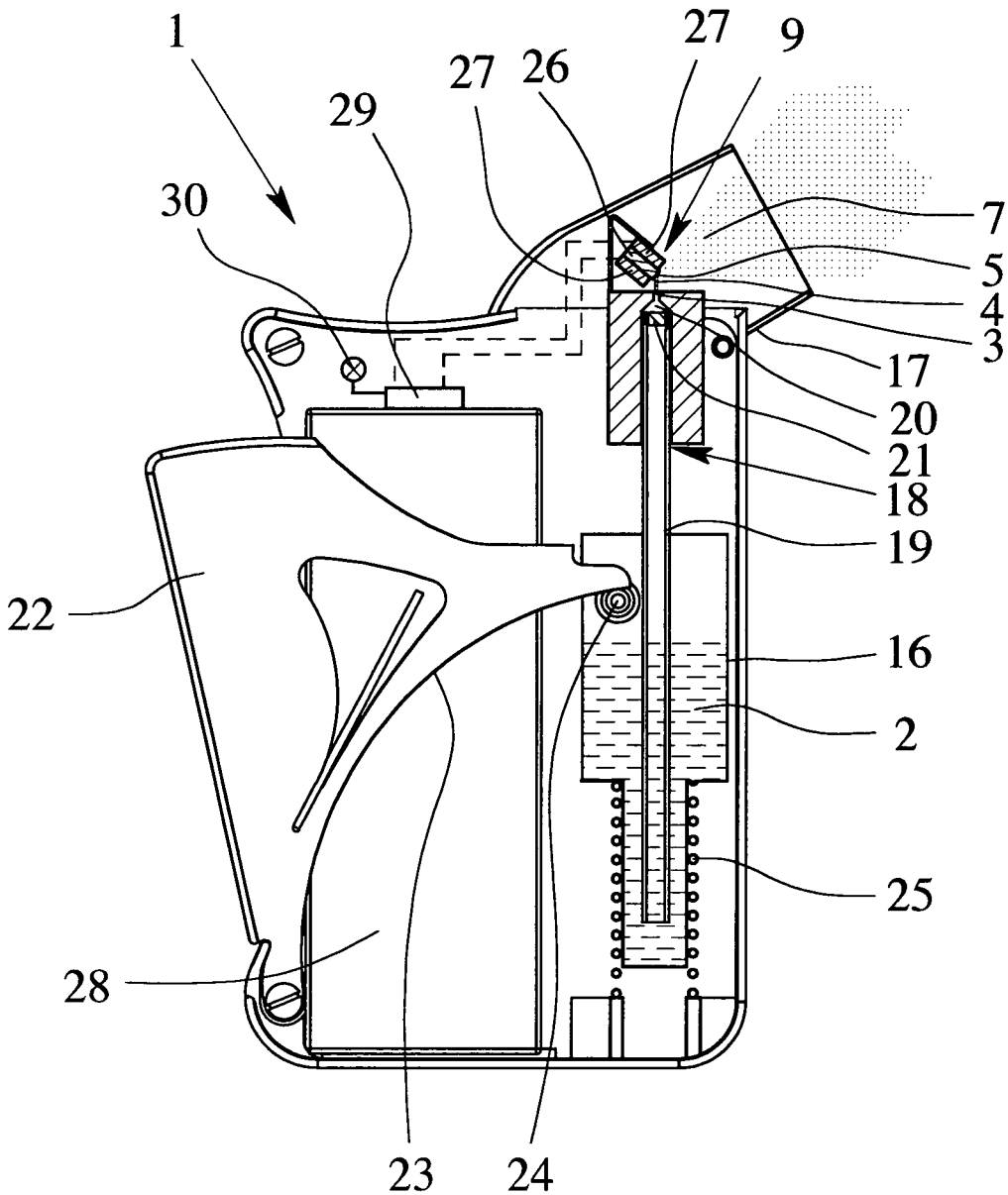


Fig. 6