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(73) Patenthaver: **Boehringer Ingelheim Microparts GmbH, Hauert 7, 44227 Dortmund, Tyskland**

(72) Opfinder: **GOLBERG, Christian, Boehringer Ingelheim International GmbH, Corporate Patents, Binger Strasse 173, 55216 INGELHEIM AM RHEIN, Tyskland**
ZUMBLICK, Ole, Boehringer Ingelheim International GmbH, Corporate Patents, Binger Strasse 173, 55216 INGELHEIM AM RHEIN, Tyskland
EICHER, Joachim Carl Herbert, , 55216 Ingelheim am Rhein, Tyskland
EIGEMANN, Jutta, , 55216 INGELHEIM AM RHEIN, Tyskland
GESER, Johannes, , 55216 INGELHEIM AM RHEIN, Tyskland
PETERS, Andreas, , 55216 INGELHEIM AM RHEIN, Tyskland

(74) Fuldmægtig i Danmark: **AWA Denmark A/S, Strandgade 56, 1401 København K, Danmark**

(54) Benævnelse: **FREMGANGSMÅDE TIL BESTEMMELSE AF EN DOSERINGSANORDNINGSFUNKTIONSMÅDE OG ANORDNING TIL UDFØRELSE AF FREMGANGSMÅDEN**

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DESCRIPTION

Method for determining the mode of operation of a metering device and device for carrying out the method

[0001] The invention relates to a method for determining the mode of operation of a metering device which serves to generate a specific single dose of an aerosol, and the aerosol contains particles of an active ingredient, wherein the particles of the active ingredient are mixed with a carrier medium to form the single dose of the aerosol.

[0002] The treatment in particular of chronic obstructive pulmonary diseases such as bronchial asthma or COPD using inhaled aerosols allows targeted drug therapy, since the active ingredient can be delivered directly to the pharmacological target site using suitable metering devices. However, the prerequisite is that the inhaled droplets or particles of the active ingredient are respirable. Only particles of a certain size range can reach the intended site of action, viz., the deep branches of the lungs (bronchioles, alveoli), in order to develop the desired therapeutic effect there.

[0003] Particles to be inhaled that are of a size of approximately 1 to 10 µm are usually considered respirable. Within this range, there are again particles that are primarily deposited in the mouth and throat by inertial impaction, and particles that are mainly influenced by gravity and are therefore ideal for deposition in the respiratory tract. However, if the particles fall below a certain size, they can be exhaled again and thus do not contribute to the desired deposition of the active ingredient in the lungs (pulmonary deposition).

[0004] For the inhalative application of active ingredients, the metering devices used today are predominantly propellant-driven metering aerosols, powder inhalers, and atomizers or nebulizers. In the case of atomizers, for example, a certain amount of (medicinal) active ingredient is stored in a

suitable reservoir; when used, a portion is taken from the active ingredient supply, atomized into an aerosol using a nozzle, and provided as a single dose. The single dose is generated or provided over a certain period of time and can then be transported in a carrier medium. The carrier medium is, for example, the ambient air inhaled by a patient.

[0005] Despite their apparent simplicity, the correct use of such metering devices is difficult because, according to current experience, most patients do not operate them correctly. This is due, among other things, to the fact that they are not able to synchronize the activation of the metering device with the inhalation and therefore do not inhale at the right time, or because they simply do not inhale deeply enough. The result is insufficient lung deposition of the active ingredient. The problem is understandably magnified in patients such as children, the elderly, and patients with reduced respiratory capacity or reduced manual ability. The problems mentioned above can be reduced by metering devices which have a sufficiently long duration for the generation of the single dose.

[0006] On the one hand, the mode of operation of a metering device should depend as little as possible upon the respective operator (patient) in order to always ensure a consistent, reproducible release of active ingredient. On the other hand, even when a metering device is used correctly, its effectiveness (achievable lung deposition of the metered active ingredient) also depends to a large extent upon the particle size distribution delivered by the metering device, which provides a measure of the aerosol or active ingredient particles, which should be within a certain size range that is respirable (as already explained above).

[0007] The particle size distribution (fine particle fraction) of the single aerosol dose (spray cloud) generated by a metering device, and the time required to generate such a single dose (spray time, i.e., time during which the spray cloud emerges from the metering device), are essential quality criteria for a metering device.

[0008] DE 101 36 554 A1 discloses a method for determining the particle size distribution in an aerosol, and a device for carrying out the method. It proposes measuring the particle size of aerosol particles simultaneously or one after the other using the laser diffraction method (also called laser diffractometry), which is well known in particle measurement technology, and the cascade impactor method, which is recognized among experts. This should make it possible to match the reliability of the results of the laser diffraction method to that of the cascade impactor, and thus combine the advantages of the fast laser diffraction method with the accuracy of the otherwise time-consuming cascade impactor method. In order to do justice to the actual conditions - in particular, the high humidity - in the human mouth, throat, and pharynx, and thus to create measurement conditions that are as close to reality as possible, it is also proposed to precondition the carrier medium with a conditioning agent.

[0009] DE 10 2007 036 412 A1 proposes a device for testing the tightness of the mouthpiece of an inhaler. Furthermore, EP 0 667 168 B1 discloses an inhalation training device designed to train a patient to effectively use an aerosol inhaler over a longer period of time. Among other things, it is proposed to provide means for recording the time of actuation of the inhaler as well as the duration of inhalation and breath-holding in order to be able to calculate the timing or time setting of actuation of the inhaler.

[0010] US2005/238588A1 concerns the determination of the size distribution of particles in an aerosol.

[0011] The invention is based upon the object of providing a method with which the operation of a metering device can be tested in a time- and cost-effective manner. Furthermore, the invention is based upon the object of providing a device for carrying out the method.

[0012] The above objects are achieved with the features of claims 1 and 8.

[0013] Advantageous embodiments or developments of the invention can be found in the respective dependent claims.

[0014] The invention proceeds from a method for determining the mode of operation of a metering device which serves to generate a specific single dose of an aerosol and which contains particles of an active ingredient, wherein the particles of the active ingredient are mixed with a carrier medium to form the single dose of the aerosol.

[0015] According to the invention, it is provided that at least the time duration for the generation of the single dose (spray time) be determined. Furthermore, in a development of the invention, the particle size distribution (fine particle content) present in the single dose is determined. Through this novel combination of the measurement or determination of fine particle content and spray time, essential quality criteria of such a metering device can be determined with just one measurement process, which allows comparatively fast and cost-effective quality control in production and, not least, in the development of such metering devices.

[0016] According to the invention, it is provided that a path measurement be carried out which measures a travel path of at least one movable component of the metering device, the movement along the travel path being necessary for the generation of the single dose. Most metering devices have at least one component that travels a specific path when a single dose is produced. Such a component can, for example, be the spray button of a spray can, which has to be pressed down a certain distance to produce a single dose, or the cartridge of an inhaler, which stores the active ingredient and which also travels a certain distance when a specific single dose is produced. Such a distance measurement is comparatively easy and reliable to carry out and therefore results in a simple and cost-effective test setup. In addition, conclusions can be drawn about the volume of active ingredient released, based upon the measured travel path over the component geometry.

Furthermore, if there are deviations from a given desired travel path, it can be concluded that there are component defects in the metering device or that component and/or assembly tolerances have been exceeded.

[0017] The invention provides that, during the path measurement, the time duration for the travel path of at least one component also be determined. Such a determination or calculation of the time period can be carried out, for example, using a suitable evaluation algorithm. This provides an easy way to draw additional conclusions as to whether system errors are present. If a measured travel path corresponds to the expected standard, but the travel time does not, this may for example indicate that the friction in the system is too high, e.g., due to too tight fits, or too low due to leakage.

[0018] According to a further embodiment of the inventive concept, the particle size distribution is measured by means of laser diffraction (laser diffractometry), and the distance/time measurement is carried out by means of laser triangulation. These are well-known and reliable measuring methods. Their use therefore contributes to reliable measurement results. These methods do not need to be explained in more detail at this point.

[0019] In order to simulate a measurement setup that is as realistic as possible, the carrier medium is preconditioned. Preferably, in this case, air is used as a carrier medium and water as a conditioning agent.

[0020] In order to reproduce a measurement setup that is as realistic as possible, it is also beneficial if at least the carrier medium is subjected to suction, and the suction is synchronized with the measurement process.

[0021] However, the invention also relates to a device for carrying out the method. According to the invention, this comprises at least one measuring cell for receiving the carrier medium and the single dose of the aerosol, at

least one first measuring apparatus, the recorded measured values of which allow a determination of the time period for the generation of the single dose (spray time), and a second measuring apparatus for measuring the particle size distribution in the single dose.

[0022] In this case, it is very advantageous if the first measuring apparatus measures the travel path, which must be covered in order to generate the single dose, of at least one component of the metering device.

[0023] When measuring the distance by the first measuring apparatus, the time duration for the travel path of at least one component is, expediently, also determined. More precisely, a sensor of the first measuring apparatus measures the travel path, and an evaluation algorithm assigned to the first measuring apparatus calculates or determines the time. Thus, essentially, a distance/time measurement takes place.

[0024] In this case, it is advantageous to use a triangulation laser in the first measuring apparatus. A particle size analyzer operating on the basis of laser diffraction can advantageously be used as a second measuring apparatus. Helium-neon lasers have proven to be cost-effective and useful here as measuring lasers, as they can emit red laser light with a wavelength of 632.8 nm and a high coherence length.

[0025] In this case, the lasers used should preferably be positioned so that the laser beams generated by the lasers are at an angle of approximately 90° to each other. This enables an uncomplicated test setup. However, depending upon the metering device to be tested, it may be expedient not only to arrange the lasers in such a way that the laser beams they generate are approximately perpendicular to each other, but it may also be advantageous if the lasers are positioned relative to one another in such a way that the laser beams they generate intersect in one plane.

[0026] In order to simulate a test environment that is as close to reality as possible, at least one conditioning apparatus can be provided which is in fluid connection with the measuring cell and provides preconditioned carrier medium in the measuring cell. Air is preferably used as the carrier medium, and water as the conditioning agent. In this case, a measurement of the air humidity can additionally be provided, e.g., by a humidity sensor, wherein, in the manner of a control loop, it is possible for a desired air humidity to be set.

[0027] Accordingly, it also contributes to a realistic test setup if at least one suction apparatus is provided which can be brought into fluid connection with the measuring cell in such a way that, during a measuring process, the fluid in the measuring cell, consisting of carrier medium and active ingredient particles, or at least the carrier medium, is suctioned off. In this case, the fluid connection can be temporally synchronized with the measurement process. For example, a controllable solenoid valve can be used for this purpose.

[0028] Further advantages and embodiments of the invention will become clear from a preferred exemplary embodiment, which will be explained in more detail with the aid of the accompanying figures, in which:

Fig. 1 is a highly schematic representation of the device according to the invention for carrying out the method according to the invention,

Fig. 2 is a path-time diagram which can be obtained during a measuring process using the device,

Fig. 3 shows a standardized series of measured values, generated using the device, from a capability study (type 1 study), which shows the respective measured fine particle content, and

Fig. 4 shows a standardized series of measured values, generated using the device, which also shows the spray time determined in the capability test according to Fig. 3.

[0029] Fig. 1 schematically shows a preferred exemplary embodiment of a device 1 for carrying out the method according to the invention. The device 1

comprises a measuring cell 2, which is essentially sealed against light and air from the environment. The measuring cell serves to receive a spray cloud 40 of an active ingredient (single dose), which has been generated by a metering device 4. For this purpose, the metering device 4 is hermetically connected to an inlet 20 of the measuring cell 2. The measuring cell 2 further comprises two translucent windows 21 and 22 through which a laser beam 31 generated by a particle size measuring device 3 can pass. More specifically, the laser beam 31 is generated by an He-Ne laser 30. The light emitted by the laser 30 falls through the window 21 into the interior of the measuring cell 2 and there strikes the generated spray cloud 40. In this case, the incident light is diffracted at the particles of the spray cloud 40, which represent an obstacle to the light. The scattered light, which is generated by the diffraction of the incident laser light on the particles of the spray cloud 40, leaves the measuring cell 2 through the window 22, is then bundled by a collecting lens 32, and fed to a semiconductor detector 33 for evaluation by suitable evaluation methods, such as the Mie method or the Fraunhofer method. Since particle size measurement using laser diffraction is known per se, it will not be discussed in more detail. It also goes without saying that appropriate evaluation computing systems must of course be provided, although these are not shown in detail in Fig. 1.

[0030] In the method according to the invention, a Respimat® brand inhaler is preferably used as the metering device 4. This is a propellant-free inhaler that produces a gentle and long-lasting spray cloud 40. Such an inhaler is disclosed, for example, in WO 97/12687. A more detailed explanation of its structure is therefore not provided. In this case, the metering device 4 has an aluminum cartridge as a movable component 41, in which an active ingredient is contained as a suspension and which serves as an active ingredient reservoir. Each time a spray cloud 40 (single dose) is generated, the component 41 executes a travel path s predetermined by the component geometry of the metering device 4, which path is delimited in Fig. 1 by the starting position of the component 41 and its end position (41'). Behind the bottom of the component 41, a measuring device 5 in the form of a triangulation laser is arranged. The measuring device

5 serves more or less for distance/time measurement and emits a laser beam 50, which is diffusely reflected (50') at the bottom of the component 41 and thus enables a laser triangulation measurement known per se. As a result, the travel path s of the component 41 is measured, and the time t required for this is calculated or determined via an evaluation algorithm assigned to the measuring device 5 (cf. Fig. 2). An He-Ne laser is again preferably used to generate the laser beam 50. Preferably, the measuring cell 2, the metering device 4 connected to it, and the measuring devices 3 and 5 are arranged in a horizontal plane.

[0031] From Fig. 1, a suction apparatus 6 can also be seen, which can be permanently switched on and is fluidically connected to an outlet 23 of the measuring cell 2. If a spray cloud 40 is now generated in the measuring cell 2 by actuating the metering device 4 (a corresponding device for facilitating actuation in the measuring setup in the form of an external switch is not shown), a measuring process is triggered, and a fluid connection between the suction apparatus 6 and the measuring cell 2 is established, only for the duration of the measuring process, by an indicated, electrically controllable solenoid valve. This results in a flow of the spray cloud 40 being generated in the direction of the suction apparatus 6 (see arrow), which runs approximately transversely to the laser beam 31 of the particle size measuring device 3.
The flow simulates a patient inhaling the spray cloud 40.

[0032] Furthermore, a conditioning apparatus 7 is shown, which has an air supply 70 and a water supply 71, wherein air and water are mixed to form humidified air with an adjustable degree of saturation at a predeterminable temperature. The conditioning apparatus 7 is connected to an inlet 24 of the measuring cell 2 so that humidified air 73 can be kept as a preconditioned carrier medium in the measuring cell 2. The aim of this is to recreate the moist oral and pharyngeal space of a patient as realistically as possible.
A humidity sensor 72 (indicated) may be provided to monitor the settings.

[0033] Finally, it should also be mentioned that the measuring devices 3 and 5 are preferably arranged such that their laser beams 31 and 50 are approximately at a right angle α to each other, which leads to a simpler measuring setup and more accurate measuring results. In the present exemplary embodiment, the arrangement is in fact such that the laser beams 31 and 50 lie approximately in one plane, and their imaginary extensions intersect.

[0034] Reference is now made to Fig. 2. This schematically shows a path/time diagram, which can be derived from the measurement of the measuring device 5. Here, the travel path s covered by the component 41 is plotted against the time t required for this. The line L represents the desired course, i.e., when the component 41 thus ideally covers a prescribed travel path s in a prescribed time t. If there are any quality defects in the metering device 4 to be tested, the measured line deviates from the desired line. For example, the following cases could occur:

- the travel path s of the component 41 is too short (s-) or too long (s+) due to excessive manufacturing and/or assembly tolerances
- the time t for the travel path s is too short (t-) or too long (t+) due to other system errors (e.g., defective nozzle or other leakage)

[0035] Due to the existing component geometry, the travel path s can also be used to determine the volume of active ingredient dispensed from the metering device 4. Similarly, conclusions can be drawn about the spraying time of the metering device 4 from the time t for the travel path s. Specifically, the time t for the travel path s corresponds approximately to the spraying time.

[0036] Finally, reference is made to Fig. 3 and 4. These represent part of the results of a so-called capability study (type 1) and show how well the method according to the invention can provide information about essential quality properties of metering devices, e.g., the metering device 4, or how well the components of the measuring device work together.

[0037] Thus, in Fig. 3 and 4, measured values of a series of measurements with the device according to the invention of more than 25 measurements are shown, wherein, in Fig. 3, the fine particle content is shown qualitatively in percent (normed) over the number of measurements carried out. In this case, 100 percent means that the desired or required minimum value has been achieved. The values achieved are clearly in a range significantly higher.

[0038] In Fig. 4, however, the spraying time is shown qualitatively in percent over the number of measurements performed. Here, 100 percent means an ideally desired spray time. The achieved values come quite close to this target value with a value of approximately 91.5%.

[0039] A further part of the capability study (type 2), which, however, is not shown in detail, showed that the method or measuring device according to the invention is essentially independent of operator influence.

[0040] Finally, it should be pointed out once again that the method according to the invention is not limited to the measurement of inhalers, but is suitable for any metering device that works in a distance-based manner, i.e., in which an active ingredient dose is dispensed based upon the distance covered by a moving component.

List of reference signs

1	measuring device
2	measuring cell
20	inlet
21	light window
22	light window
23	outlet
24	inlet
3	particle size measuring device
30	laser of the particle size measuring device
31	generated laser beam
32	lens
33	semiconductor detector
4	metering device
40	generated spray cloud of the active ingredient (single dose)
41,41'	movable component of the metering device
5	distance/time measuring device
50	generated laser beam
6	suction apparatus
60	solenoid valve
7	conditioning apparatus
70	air supply
71	water supply
72	humidity sensor
73	humidified air
α	angle at which the laser beams of the measuring devices are positioned relative to each other
s	travel path of the moving component
$s_{desired}$	desired travel path of the moving component
L	desired line in the path/time diagram
s+	distance/time diagram with excessive distance

s- distance/time diagram with too small distance

t time required for the moving component to cover the travel path

$t_{desired}$ desired time for the moving component to cover the travel path

t+ distance/time diagram with excessive time requirement

t+ distance/time diagram with too low a time requirement

P A T E N T K R A V

1. Fremgangsmåde til bestemmelse af en doseringsanordningsfunktionsmåde (4), hvilken anvendes til fremstilling af en specifik individuel dosis (40) af en aerosol, og aerosolen indeholder partikler af et aktivt stof, hvor partiklerne af det aktive stof blandes med et bæremiddel (73) for at danne den individuelle dosis (40) af aerosolen, hvor tidsperioden (t) for fremstillingen af den individuelle dosis (40) udregnes, kendetegnet ved, at der udføres en lasertrianguleringsmåling, hvor en bevægelsesbane (s) for mindst en bevægelig bestanddel (41, 41') af doseringsanordningen (4), der skal dækkes for at danne den individuelle dosis (40), måles, og tidsperioden for bevægelsesbanen (s) udregnes.

2. Fremgangsmåde ifølge krav 1, kendetegnet ved, at fremgangsmåden omfatter en bestemmelse af partikelstørrelsesfordeling.

3. Fremgangsmåde ifølge krav 1 eller 2, kendetegnet ved, at doseringsanordningen (4) omfatter en patron som en bevægelig bestanddel (41), der fungerer som et aktivt stofreservior.

4. Fremgangsmåde ifølge 1, 2 eller 3, kendetegnet ved, at bevægelsesbanen (s) og tidsperioden (t) sammenlignes med en mål-bevægelseslinje (L), for at fastslå kvalitetsfejl i doseringsanordningen.

5. Fremgangsmåde ifølge krav 2, kendetegnet ved, at partikelstørrelsesfordelingen i den individuelle dosis (40) beregnes ved hjælp af laserdiffraktion.

6. Fremgangsmåde ifølge mindst et af de foregående krav, kendetegnet ved, at bæremidlet (73) fugtes.

7. Fremgangsmåde ifølge mindst et af de foregående krav, kendetegnet ved, at mindst bæremidlet (73) udsættes for sugning, og at sugningen er synkroniseret med måleprocessen.

8. Anordning (1) til udførelse af fremgangsmåden ifølge mindst et af de foregående krav, med mindst en målecelle (2) til at modtage bæremidlet (73) og den individuelle dosis (40) af aerosolen, mindst en måleanordning (5), som måler en bevægelsesbane (s) for mindst en bevægelig bestanddel (41) i en doseringsanordning (4), hvor bevægelsesbanen (s) skal tilbagelægges for at danne den individuelle dosis (40), og de målte værdier fra måleanordningen (5) muliggør en bestemmelse af tidsperioden (t) for dannelsen af den individuelle dosis (40), hvor der anvendes en trianguleringslaser i måleanordningen.

9. Anordning ifølge krav 8, kendetegnet ved, at måleanordningen (5) beregner tidsperioden (t) for den mindst ene bestanddels (41) bevægelsesbane (s) via en tilknyttet evalueringsalgoritme.

10. Anordning ifølge mindst et af foregående krav 8 eller 9, kendetegnet ved, at anordningen omfatter en anden måleanordning (3) til måling af partikelstørrelsesfordelingen i den individuelle dosis (40).

11. Anordning ifølge krav 10, kendetegnet ved, at den anden måleanordning (3) er en partikelstørrelsesanalysator, der fungerer efter principperne for laserdiffraktion.

12. Anordning ifølge krav 11, kendetegnet ved, at laserstråler (31, 50), der dannes af måleinstrumenterne (3, 5), står i en vinkel på ca. 90° i forhold til hinanden.

13. Anordning ifølge mindst et af kravene 8 til 12, kendetegnet ved, at der er tilvejebragt mindst én konditioneringsanordning (7), som er i fluidisk forbindelse med målecellen (2) og tilvejebragt et forkonditioneret bæremiddel (73) i målecellen (2).

14. Anordning ifølge mindst er af kravene 8 til 13, kendetegnet ved, at der er tilvejebragt en sugeanordning (6), som kan bringes i fluidisk forbindelse med målecellen (2) på en sådan måde, at den fluid, der er tilstede i målcellen (2), suges af under en måleproces.

15. Anordning ifølge krav 12, kendetegnet ved, at laserstrålerne (31, 50) skærer hinanden i et plan.

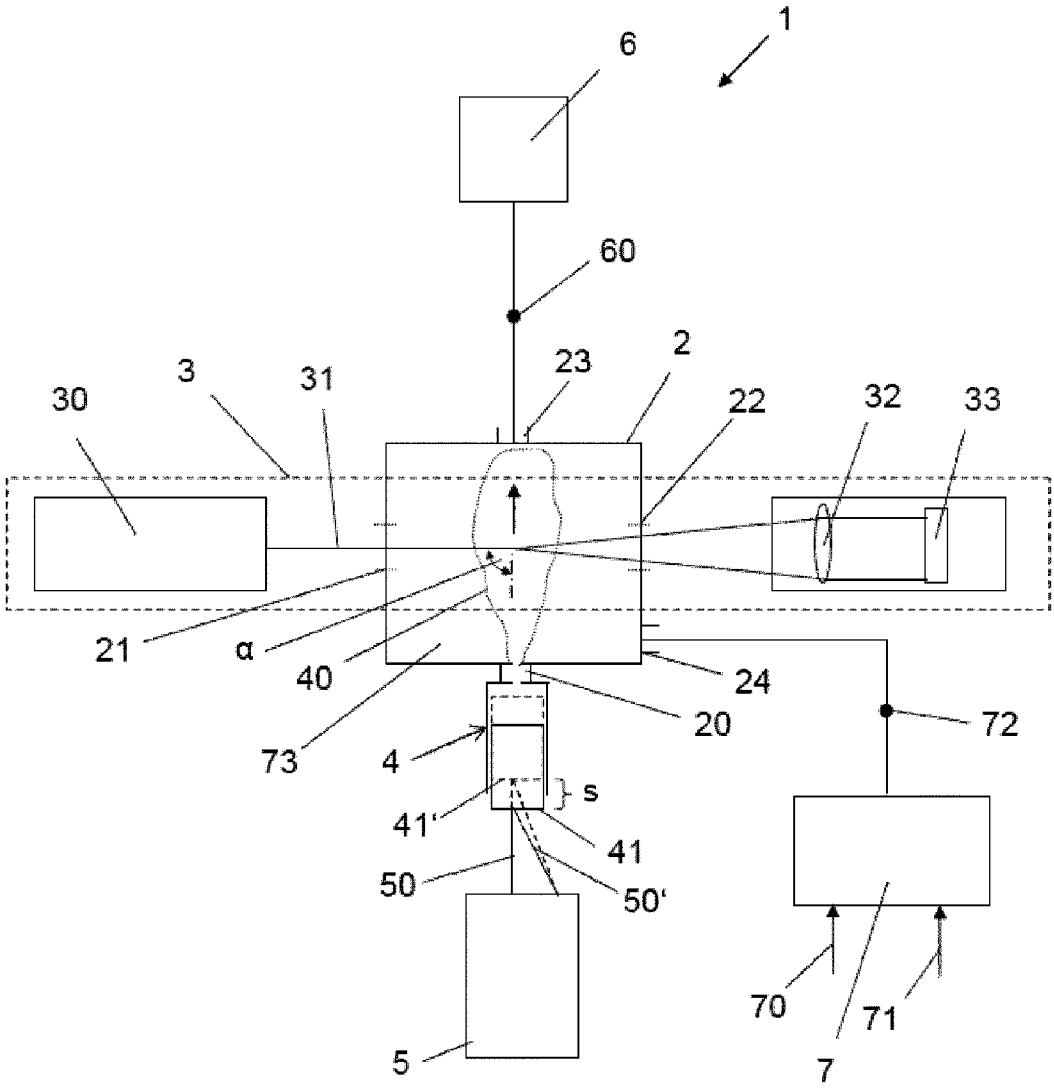

Fig. 1

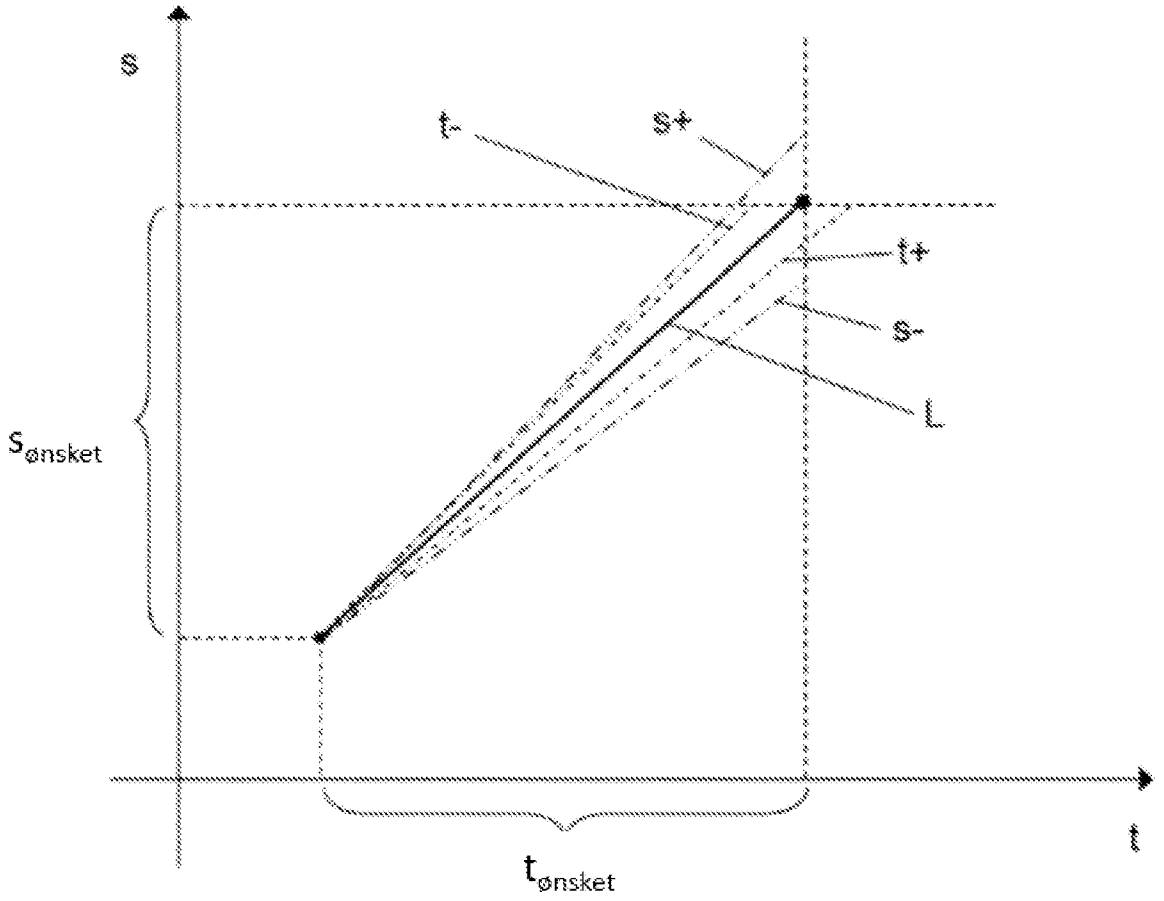

Fig. 2

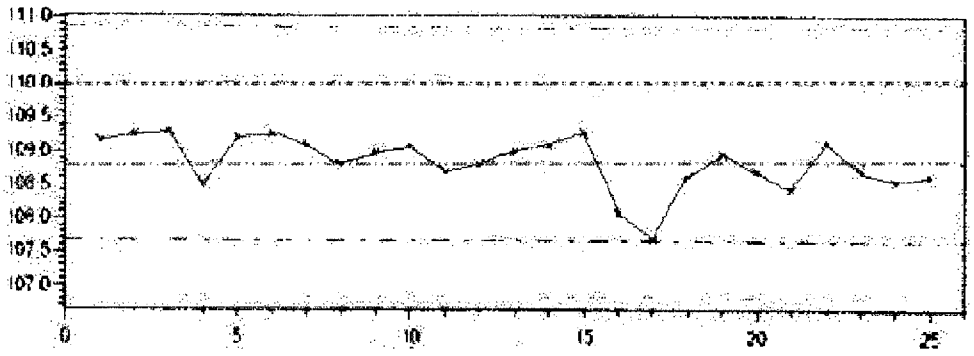
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Fig. 3

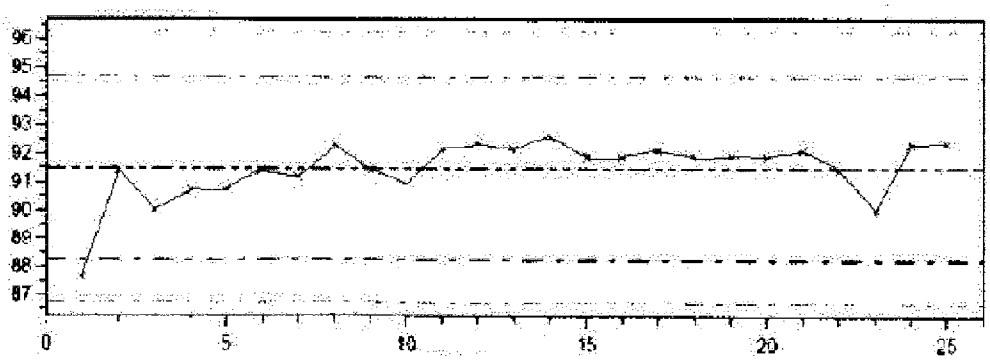
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Fig. 4