DEVICE IN INHALERS

Technical field of the invention

The present invention relates to an inhalation device comprising means for breaking down aggregates of finely divided powdered medicament having a particle size less than 10 µm to provide a finely divided medicament having a large amount of particles within the respiratory range, i.e. having particle sizes less than 10 µm.

Background to the invention

In inhalation therapy it is of utmost importance that the diameter of particles of the medicament to be inhaled is less than 10 µm to ensure the adequate penetration of the particles into the bronchial region of the lungs.

For particles having a diameter less than 10 µm the interparticular forces are generally greater than the force of gravity and consequently the material is cohesive. Non-defined agglomerates or aggregates are formed at random when this finely divided powdered medicament is handled, for instance during storage, conveying, sieving, sifting, mixing or grinding.

When using dry powder inhalers and especially breath-actuated dry powder inhalers it is therefore important that the inhalation device is provided with means which break down just before or during inhalation the said agglomerates or aggregates formed from the finely divided powder into the primary particles having a particles size within the respiratory range, of less than 10 µm, preferably less than 5 µm.

If the particles are bigger than 10 µm they will not penetrate to the bronchial region of the lungs but will end up in the oro-laryngeal tract or, if swallowed, in the gastrointestinal tract where they could lead to unwanted side-effects. Particles could more easily be retained in

the device which also leads to a loss of particles which will have a negative effect on the exactness of the doses.

Prior art

Means for breaking down agglomerates/aggregates of powder created in finely divided powdered medicaments having a particle size less than 10 µm are known in the prior art. One example of such means is described in EP-B-069 715. In this document a rotating, propeller-like device is provided in the air conduit as deagglomeration means. Another example is described in EP-B-237 507, where a stationary deflector device is provided in the mouth-piece and/or the air conduit of a breath-actuated dry powder inhaler having a container for multiple doses. These stationary deflector devices will, during inhalation, provide a deaggregating effect as they are constructed to create a turbulent movement in the air flow carrying the substance. Due to this turbulent movement the particles will impact on the walls of the air conduit and the deflector devices and collide with each other and in this manner break down into particles within the respiratory range.

In WO 92/04069 a disposable breath-actuated dry powder inhaler for single use is disclosed. This inhaler is provided with means for breaking down agglomerates /aggregates in the air conduit. The deagglomerating means are also in this inhaler constructed to create a turbulent movement in the air flow during inhalation. This is achieved as all of the deagglomerating means are constructed as planar surfaces oriented about 30° relative to the longitudinal direction of the tubular housing of the inhaler.

Tests have shown that the above mentioned deaggregation means do not give an optimum deaggregation effect. In some cases retention in the inhaler could reach an unacceptable level. This could lead to different dosages with different inhalations.

The invention

It is therefore an object of the present invention to provide deaggregation means which optimize the deaggregation and which minimise the retention and the flow resistance at a typical gas or air flow rate which depends on the inhalation force of a patient.

According to the present invention there is provided an inhalation device comprising means for breaking down aggregates, the device being characterised in that said means comprise at least one pair of surfaces in a gas/air flow path, the first surface of the pair providing an inlet surface of a constriction in the gas/air flow path whereby the speed of gas/air passing along the flow path through the constriction is increased, and the second surface of the pair is situated at or near the outlet of the constriction and provides an impact surface so that in use aggregates or particles impact said second surface whereby said first and second surfaces are oriented at different angles to the longitudinal direction of the flow path and whereby said first and second surfaces are oriented at different angles to the longitudinal direction of the flow path.

Further preferred embodiments and adavantages are clear from the depending claims 2 to 11.

Brief description of the drawings

The device according to the present invention will now be described by way of example with reference to the appended drawings, wherein

Figure 1 shows a preferred embodiment of the deaggregation means according to the present invention;

Figure 2 shows first deaggregation means according to the invention as shown in figure 1; and

Figure 3 shows the two bodies of the second deaggregation means according to the invention as shown in figure 1.

Detailed description of the drawings

It is generally known in powder technology that the breakdown of aggregates formed from powdered substances can be achieved by giving aggregates an acceleration prior to impact with a surface, for example walls placed in the direction of the movement of the aggregates. When this technology is applied to inhalation materials so-called deaggregation means are placed in the gas/air flow path of the inhalation device. Such deaggregation means can be provided as walls, as described in the above mentioned documents.

Tests have shown that the breakdown of aggregates into primary particles is related to the positions and angles of said surfaces as well as the dimensions of the cross sections of gas/air flow path of the inhaler at different positions. A preferred embodiment of deaggregation means in accordance with the present invention will be described with reference to figures 1, 2 and 3.

The deaggregation means of the present invention are in the preferred embodiment designed to be placed in the gas/air flow path of a unit dose dry powder inhaler but the construction of the deaggregation means could easily be adapted to be placed in the gas/air flow path of any dry powder inhaler having a dose 8 which comprises aggregates of a powdered substance placed in an gas/air flow path 10, an air inlet 5 and an air outlet 6. Said air inlet 5 and air outlet 6 are positioned at a distance from each other, whereby the gas/air flow during inhalation will pass in said gas/air flow path between the air inlet and the air outlet thereby lifting the dose so that it can be carried along by the gas in the gas/air flow. The description of the device is related to this embodiment but this is only given as an example and for the matter of clarity.

In the preferred embodiment several sets of oblique planar surfaces are provided along the gas/air flow path 10 in the inhaler. The dose 8 is placed in a magazine (not shown) which could be a unit dose magazine or a magazine which could be refilled for the following inhalations.

Said oblique surfaces provide constrictions in the gas/air flow path which will result in an acceleration of the inhalation gas/air flow and guidance during its passage through the gas/air flow path. The aggregates and/or particles will thereby be forced to impact on the walls and surfaces of the gas/air flow path.

In the preferred embodiments the deaggregation means have substantially two different forms and constructions.

As shown in Figures 1 and 2, the first deaggregation means 20 and 30 are formed as pairs of walls 21a, 21b and 31a, 31b respectively extending with an angle α_a and α_b, respectively, to the main direction (Arrow A in the figures) of the gas/air flow and the longitudinal centre axis of symmetry of the gas/air flow path 10 and the device seen from the air inlet to the air outlet. Said longitudinal centre axis is marked with X-X in figures 1-3. Preferably said pairs of walls extend from the edges of the housing on both sides of the gas/air flow path symmetrically and are spaced apart so as to provide a passage for the gas/air flow and a restriction in the gas/air flow path. The first pair of walls 21a, 21b are placed adjacent the release area of the dose 8. Said pairs of walls 21a, 21b and 31a, 31b are connected to a part 22a, 22b and 32a, 32b respectively being longitudinal in the main direction A of the gas/air flow. Said longitudinal parts extend parallel to the main direction A of the gas/air flow and are spaced apart so as to provide a passage for the gas/air flow. The other end of said longitudinal parts 22a, 22b and 32a, 32b are connected to a wall 23a, 23b and 33a, 33b respectively which together with the first wall and the longitudinal part of each deaggregation means form a quadrangle 20, 30 respectively. In figures 1 and 2 a preferred embodiment of these first deaggregation means are shown. The angle and form of the walls 23a, 23b and 33a, 33b are only of importance for the construction and geometry of the

deaggregation means and the gas/air flow path and is not important for the function of the device. The important feature for the function is the aim to minimise the retention of substance in the gas/air flow path. Therefore any angle and/or form of said walls having this function can be used.

The second deaggregation means 40, 50 are formed as pairs of walls 41a, 41b and 51a, 51b respectively. The two walls in each pair of walls are connected to each other and form a tip or point 42, 52 respectively. Said tip or point 42, 52 is provided in the centre of the gas/air flow path 10 and coincides with the longitudinal axis of symmetry X-X of the gas/air flow path and also with the main direction A of the gas/air flow seen from the air inlet 5 to the air outlet 6.

In the preferred embodiment said second deaggregation means 40, 50 are formed as quadrangles being symmetrical around their longitudinal axis Y-Y as can be seen in figures 3. Said quadrangles will thereby be formed so that the longitudinal axis of each quadrangle will be parallel and in the preferred embodiment coincide with the longitudinal axis of symmetry X-X of the gas/air flow path.

The impaction surface 41a, 41b and 51a, 51b of said deaggregation means are provided at angles β and δ, respectively, to the main direction A of the gas/air flow and the longitudinal axis of symmetry X-X of the gas/air flow path and the device seen from the air inlet 5 to the air outlet 6. The preferred embodiment of the second deaggregation means 40 and 50 are shown in figure 3.

The first and second deaggregation means 20, 30 and 40, 50 are positioned in the gas/air flow path in a manner which give rise to acceleration areas for the gas/air flow and the aggregates/particles as well as guidance whereby the aggregates and particles are forced to impact on the walls of said deaggregation means.

The form of the deaggregation means has been determined by tests and the most optimal forms for the above mentioned purpose have shown to be the ones represented in figure 1. The forms of the deaggregation means are also of importance for retention of substance in the gas/air flow path as well as for the gas/air flow resistance of an inhaler in which the deaggregation means are provided. For example if the deaggregation means are formed as triangles with the tip of the triangles facing the direction of the air flow during inhalation the backside of the means will have a generally flat surface positioned perpendicular to the inhalation air flow. This will give rise to substantial retention.

The tests have shown that the values of the angles α_a, α_b and especially the values of the angles β and δ are of utmost importance for good functioning of the deaggregation means and thereby the functioning of the inhaler. Several tests have been done with different substances and the values of the angles have been determined of an optimization of the different parameters which influences the performance of the gas/air flow during inhalation. It has thereby been important to minimise retention of substance and the flow resistance as well as maximise the deaggregation at a typical gas/air flow rate which depends on the inhalation force of a patient.

The earlier tests have shown that the α_a and α_b should be substantially about 30° to the main direction of the gas/air flow seen from the air inlet to the air outlet and to a longitudinal axis being parallel to the longitudinal axis of symmetry of the device. The choice of 30° for these angles is dependent on minimising the flow resistance and retention of substance as well as optimising the acceleration of the air/gas flow upon entry into the first constriction in the gas/air flow path.

The value of the angle β is substantially about 45° to the main direction of the gas/air flow seen from the air inlet to the air outlet and to the longitudinal axis of the device.

The value of the angle δ is substantially about 60° to the main direction of the gas/air flow seen from the air inlet to the air outlet and to the longitudinal axis of the device.

The choice of these values is based on test results, a summary of which is shown below.

Summary of the results from tests carried out in order to determine the optimum values of the angles β and δ:

Several tests have been carried out in order to decide the optimum values of the angles of the second and third deagglomeration means, i.e. the angles β and δ. Below a summary of the results from these test are shown in tables.

In all tests the first angles α_a and α_b have been kept constant at 30° in order to provide a smooth entry for the air/gas flow into the air/gas flow path. Tests were carried out using substances having different properties and the substances used in each test is indicated in the table.

In order to be able to compare the results from the different tests an index was introduced. Said index is based on the following calculation:

$$I = (F^2 \div (Re * C)) * 10000$$

where I is the Index, F is the fraction of fine particles, Re is the retention in percentage of total dose, and C is the inhalation resistance (C-value). By multiplying the result with 10000 an "easy-to-read" value was provided.

Study 1.

Table 1

In this study one substance - Terbutalinesulphate - was used and the aim of the tests was to determine the relationship between the values of the angles β and δ.

Test No.	Value of angles α_a, α_b	Value of angle β	Value of angle δ	Fraction of fine particles (F)	Retention (% of total dose)	Inhalation resistance (C-value)	Index (I)
1	30°	75°	60°	44	18	15395	70
2	30°	45°	60°	44	15	14424	89
3	30°	75°	21°	36	18	14765	70
4	30°	45°	21°	35	14	12488	49
5	30°	60°	30°	43	21	12825	69

As can be seen test no. 2 with β being 45° and δ being 60° showed the highest index. On the other hand test no. 4 with β being 45° and δ being 21° showed the lowest index. This indicates that $\beta < \delta$ is more favourable then $\beta > \delta$.

Study 2.

In this test three different substances was tested Terbutalinesulphate, Budesonide, and Formoterol mixed with Lactose. The aim of the tests was to determine whether an optimum value of the angles could be found in the range 21° - 75°.

Table 2

Substance: Terbutalinesulphate

Test No.	Value of angles α_a, α_b	Value of angle β	Value of angle δ	Fraction of fine particles (F)	Retention (% of total dose)	Inhalation resistance (C-value)	Index (I)
1	30°	21°	21°	24	8	10630	71
2	30°	75°	21°	24	11	11110	50
3	30°	45°	45°	32	11	12420	76
4	30°	21°	75°	37	12	13120	86
5	30°	75°	75°	40	11	14000	107

Table 3

Substance: Budesonide

Test No.	Value of angles α_a, α_b	Value of angle β	Value of angle δ	Fraction of fine particles (F)	Retention (% of total dose)	Inhalation resistance (C-value)	Index (I)
1	30°	21°	21°	17	12	10630	22
2	30°	75°	21°	22	22	11110	20
3	30°	45°	45°	27	17	12420	36
4	30°	21°	75°	37	28	13120	39
5	30°	75°	75°	43	31	14000	42

Table 4

Substance: Formoterol mixed with Lactose

Test No.	Value of angles α_a, α_b	Value of angle β	Value of angle δ	Fraction of fine particles (F)	Retention (% of total dose)	Inhalation resistance (C-value)	Index (I)
1	30°	21°	21°	31	16	10630	58
2	30°	75°	21°	42	28	11110	58
3	30°	45°	45°	49	21	12420	90
4	30°	21°	75°	51	27	13120	74
5	30°	75°	75°	63	30	14000	86

The result of these tests also showed that $\beta < \delta$ gave a better result than $\beta > \delta$. The value of β does not influence the result to a significant extent but the result for $\beta = 45°$ and $\delta = 45°$ was better than expected. In fact this was the best one for the substance Formoterol mixed with Lactose.

The results obtained in the first two studies show that 45° seem to be the optimum for the angle β.

Study 3.

This study was carried out in order to determine the upper limit of the value of the angle δ. The substances used was conditioned and unconditioned Terbutalinesulphate

Table 5

Substance: conditioned Terbutalinesulphate

Test No.	Value of angles α_a, α_b	Value of angle β	Value of angle δ	Fraction of fine particles (F)	Retention (% of total dose)	Inhalation resistance (C-value)	Index (I)
1	30°	45°	60°	49	14	13342	129
2	30°	45°	70°	49	20	14825	81
3	30°	45°	75°	52	17	15502	103
4	30°	45°	80°	50	22	15183	75
5	30°	45°	85°	52	23	15482	76
6	30°	45°	90°	26	16	15872	83

Table 6

Substance: unconditioned Terbutalinesulphate

Test No.	Value of angles α_a, α_b	Value of angle β	Value of angle δ	Fraction of fine particles (F)	Retention (% of total dose)	Inhalation resistance (C-value)	Index (I)
1	30°	45°	60°	53	11	13342	191
2	30°	45°	75°	49	12	15502	129
3	30°	45°	90°	55	13	15872	147

The result of these tests also showed that the best results are achieved with the values of the angles β and δ being 45° and 60°, respectively.

The results of the above described tests gave the basis for choosing the following values on the angles in the inhalation device according to the present invention:
α_a and α_b being 30°, β being 45° and δ being 60°.

The device according to the invention is simple to produce. It is preferably produced in two pieces, a first substantially flat part and a second part in which the air flow path with the constrictions and the deaggregation parts is formed during a moulding or cold forming procedure. The two parts are then connected to each other in manner that provides a air tight seal between the two parts. For this purpose heat- or cold-sealing, laser-welding or ultra sonic welding could be used as well as any other suitable sealing method. The two parts of the device are preferably made of plastic material but any other material in which the required air flow path can be easily formed can be used. The device could also be formed by two identical parts which are sealingly connected to each other. This is however a more complicated method.

It is also possible to produce the device in one part whereby injection moulding or blow molding could be used.

Modifications

The device according to the invention as described above can of course be modified within the scope of the appended claims.

Thus in the preferred embodiment the first and second deagglomeration means are formed as quadrangles having the described form. It is however clear that the form of the deagglomeration means can be varied. For example, the "backside" of the deagglomeration means can have any form which preferably does not give raise to a significant reduction in the speed of the gas/air flow or substantial retention of substance as mentioned above. The second deagglomeration means could for example be formed as triangles or being V-formed whereby the top of the triangle or the tip of the V is placed in the center of the gas/air flow path of the device.

The values of angles α_a, α_b and β, δ could be changed although the performed tests show that the most optimate value of these angles are the ones as stated above.

Furthermore, it is easy for the man skilled in the art to realise that the deaggreagtion means as described above and as claimed in the appended claims can be modified to be used in any powder inhaler, in particular dry powder inhalers.

Claims

1. An inhalation device comprising means (20; 30; 40; 50) for breaking down aggregates of finely divided powdered medicament having a particle size less than 10 µm to provide a finely divided medicament having a large amount of particles within the respiratory range, i.e. having particle sizes less than 10 µm,
c h a r a c t e r i s e d in that said means (20; 30; 40; 50) comprise at least one pair of surfaces in a gas/air flow path, the first surface of the pair providing an inlet surface of a constriction in the gas/air flow path whereby the speed of gas/air passing along the flow path through the constriction is increased, and the second surface of the pair is situated at or near the outlet of the constriction and provides an impact surface so that in use aggregates or particles impact said surfaces, and whereby said first and second surfaces are oriented at different angles to the longitudinal direction of the flow path.

2. A device as claimed in claim 1 wherein there is present at least two pairs of said surfaces (40, 50) in series so that aggregates or particles of medicaments when the device is in use impact upon two impact surfaces situated at or near the outlet of at least two constrictions wherein the volume for the gas/air between the two constrictions is arranged such that the speed of the gas/air along the flow path from the first constriction is reduced before the speed of the gas/air is further increased as a result of passage through the second constriction.

3. Device in inhalers according to claim 2,
c h a r a c t e r i s e d in that first deaggregation means (20, 30) are provided as pairs of planar surfaces or walls (21a, 21b; 31a, 31b) extending from the edges of the housing on both sides of the gas/air flow path and oriented at an angle α_a, α_b respectively, relative to the longitudinal direction of the housing (1) seen from the air inlet (5) to the air outlet (6).

4. Device in inhalers according to claim 3,
characterised in that the angle α_a, α_b is preferably substantially about 30°.

5. Device in inhalers according to claim 4,
characterised in that second deaggregation means (40, 50) are provided as pairs of planar surfaces or walls (41a, 41b; 51a, 51b) positioned symmetrically around the longitudinal centre axis of the housing (1) and oriented at angles β and δ respectively, relative to the longitudinal direction of the housing (1) seen from the air inlet (5) to the air outlet (6).

6. Device in inhalers according to claim 5,
characterised in that the angle β is preferably substantially about 45° and in that the angle δ is preferably substantially about 60°.

7. A device as claimed in any one of the preceding claims which is disposable and substantially made of plastics material.

8. A device as claimed in claim 7, which is a dry-powder inhaler containing at least one dose of a medicament for use in treatment of a disease.

9. A device as claimed in claim 7 or 8, wherein there is a magazine to hold a purality of doses of medicament.

10. A device as claimed in any of claims 7, 8 or 9, wherein the medicament comprises one active ingredient and a carrier therefor.