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The invention relates to an apparatus and processes for metering small amounts of finely divided powder.

Small amounts of finely divided, preferably micronised powder are used particularly for therapeutic purposes, mainly in the form of aerosols for the treatment by inhalation of respiratory complaints such as asthma.

An apparatus of this kind is known from DE-A-1792201.

Powders of this kind are conveyed to the patient's lungs in amounts which are usually well below 50 mg in the air breathed in. It has been found that the particles of active substance should be less than 10 μm in size to ensure that they penetrate deep into the lungs. However, this does not rule out the use of some larger particles in the preparations, particularly for any excipients. If particles of different sizes are used, a significant difference in size is sometimes even desirable or in any case not harmful.

Two main methods have been developed for administering fine powders without the aid of propellant gases in respiratory tract therapy.

One method makes use of hard gelatine capsules each of which contains a dose of active substance and possibly also excipients, whilst the other, using a measuring chamber, removes a specific amount of powder from a storage container and mixes it with the air breathed in. Devices for both methods have been described in large numbers, cf. for example DE-OS 23 46 914; EP-OS 166 294.

The invention now provides a new method of administering fine powders. In this method, the ease of manufacture of carriers charged with active substance is advantageously combined with accuracy of metering and

the possibility of producing an aerosol suitable for inhalation by simple means.

According to the invention, a velour or velvet-like material is charged with the powder which is to be metered and the desired amount of powder is blown down from the carrier by means of a gas jet, possibly after mechanical loosening, preferably using an air jet of suitable intensity. When used for inhalation, the powder released is mixed with the air breathed in, optionally via an inhalation device such as the one described for example in German Utility Model 89 08273.

The PCT application WO 90/13328 filed within the priority interval of the present application proposes elongate carriers charged with inhalable powders. Carriers with a velour or velvet-like structure are not mentioned, however.

When the dry powder is spread into the velour material, the movement of the fibres under the doctor blade causes a preliminary break-up. The particles are then in a very loose state and are correspondingly less inclined to clump together. When the powder is applied by means of a suspension, this preliminary break-up is achieved by running an edge over the powder, so that once again only some of the energy for the breaking-up has to be supplied by the gas jet. Moreover, the previously broken up particles present a large surface area for contact with the gas jet, which again has a favourable effect on dispersal.

The carrier consists of a substantially planar material on which thin fibres are provided. The fibres are secured by one end or at the centre on or in the carrier, the free end or the two free ends being directed upwardly and the carrier and fibres predominantly forming angles of 45 to 90°, more particularly 60 to 90° with one another. The material which carries the fibres may be, for example, paper, plastics film or a textile fabric; the fibres may be

natural or synthetic, e.g. cotton, wool, silk, viscose, perlon, nylon or polyacrylic.

The fibres are up to about 3 mm long, preferably up to about 1 mm long. They should not be too matted, to ensure that the powder applied, which is essentially embedded between the fibres, can be blown out again relatively easily. The lower limit for the length of the fibres is about 0.1 mm. Generally, the length of the fibres should be such that the powder applied can be accommodated in the desired quantities per unit of surface area.

Accordingly, a carrier material with longer fibres is appropriate for relatively large quantities of powder per unit of surface area, whereas, for very small quantities of powder per unit of surface area, shorter fibres are usable or, even, advantageous. The quantity of powder which can be applied per unit of surface area depends mainly on the nature (density) of the powder and its compaction, as well as the carrier material used. If the powder is to be administered by inhalation, care must however be taken to ensure that the dispersal of the powder in the gas or air jet used is not affected by excessive compaction.

The number of fibres per unit of surface area may vary considerably. Various commercially available carriers have proved suitable (velour-film, velvet, niki). These products also provide a guide to the suitable fibre density of other carriers. The fibre thickness also varies within wide limits. Generally, fibres with a diameter of from 0.002 to 0.05, preferably 0.004 to 0.03 mm are used. The velvet-like carrier itself may also be attached, e.g. by glueing, to a stiff layer. It is also possible to attach an absorbent under-layer.

The carrier may be correspondingly flexible or rigid and rectangular or circular, for example. Preferably, the carrier is in the form of a strip. This

may be charged with the powder over its entire surface or over individual areas. In the latter case, the strip may be charged with the powder by means of a template over small individual areas, e.g. in the form of circular areas a few millimetres in diameter and clearly spaced apart, so that when the powder is blown out from one of these areas the powder on the neighbouring areas remains unaffected.

Thus, the dose can be accurately fixed by means of the quantity of powder on each of the small charged areas.

If the entire surface of the carrier is coated with powder, the quantity of powder which is blown out can simply be determined by the size of the area exposed to the gas jet during each separate removal operation and defined, for example, by means of a mask. However, a mask is not essential. It has been found, in fact, that the quantity of powder blown downwards from the uniformly charged carrier by means of the gas jet is substantially constant. Consequently, the quantity of powder dispersed can also be regulated by the intensity of the gas jet and the geometry of the nozzle.

In order to protect the layer of powder it may be appropriate to cover or laminate the carrier with a plastics film, for example, in such a way that only that part of the carrier from which powder is to be taken is exposed. Particularly in moisture-sensitive powders, an aluminium lamination on both sides might be considered. Finally, it is also possible to use carriers, e.g. strips, in which there are alternating areas filled with fibres and smooth areas.

In order to charge the carrier, first of all a layer of powder 1 to 2 mm high is distributed as uniformly as possible thereon (in the case of highly effective pharmaceutical powders and in the case of carriers with very short fibres the layer may be considerably thinner). The powder is pressed into the

strip by means of a doctor blade and excess powder is wiped away. This process is repeated once or several times, as necessary, with the doctor blade being set progressively lower. As a result of the movement of the fibres under the pressure of the doctor blade, the agglomerated areas of powder are broken up.

If only certain parts of the carrier are to be charged, the carrier may be covered, for example, with a template, e.g. a suitably perforated film. If the powder is then applied as described above, the carrier will be charged with it only at those points where the perforations are located.

The powder may also be applied to the carrier in the form of a suspension. In the case of pharmaceutical compositions for inhalation, the dosage of active substance is generally so small that the quantity of active substance contained in one drop of suspension is sufficient. One drop of the suspension is then applied at the desired spacing from the next drop. The spacing is selected so that the spot of powder which remains after evaporation of the suspension agent is clearly separated from the adjacent spot. The aim is to be able to separate only the exact quantity of powder applied in one drop from the carrier when the powdered active substance is transferred into the stream of air breathed in.

It is particularly satisfactory to charge the carrier with an accurately metered quantity of powder over a small area using a suspension.

The suspending agents used may be liquid organic compounds in which the powder to be applied does not dissolved readily and which can be eliminated as completely as possible.

Examples of suspending agents of this kind which are selected in accordance with the solubility characteristics of the substance or mixture of substances to be suspended include dichloromethane,

ethyl acetate, 1,1,1-trichloroethane or petrol (e.g. the fraction 60/95 or 80/110). As a rule, suspension adjuvants such as lecithin are added to the suspension. The solids content in the suspension is usually between 3 and 30 percent by weight, preferably from 5 to 25 percent by weight; the quantity of suspension adjuvants varies between about 0.5 and 3 percent by weight, based on the solids.

The carriers and suspension should be such that the particles of powder are left behind at the point where the drop penetrates into the carrier, whilst the suspending agent spreads out and then evaporates. The evaporation can be promoted by pressure reduction and/or by heating.

The material from the dried drop of suspension cannot generally be released and dispersed simply by means of a jet of air. However, if the fibres of the carrier are moved, e.g. by running an edge over them the bonds between the particles of powder are broken up again and the powder is "activated". The individual particles which adhere to one another or to the fibres of the carrier with only slight adhesive force after activation can then be released by means of an air jet and dispersed, to a large extent, into the lungs.

Instead of releasing the loosened powder from the carrier by means of a jet of air, it is also possible to loosen it by running an edge over it or by brushing, immediately before or while the flow of breathed-in air is passing the carrier, and thereby transferring the powder into the air which is breathed in.

Apart from the high degree of accuracy of metering, the application of a drop of suspension has the further advantage over the application of dry powder that the powder is protected from being released by acceleration (impact, vibrations) by the incrustation. The activation by running along an edge should only be carried out immediately before the powder is released

for inhalation.

An apparatus for applying the drop of suspension according to the invention is diagrammatically shown in Figure 1. The suspension 1 is initially in the storage container 2. From there it flows through the line 3 to a magnetic valve 4 and passed the valve surfaces through the line 5 into the storage container 6. In the resting position the plunger 7 seals off the inlet port of the line 8 from which the suspension is applied to the carrier 11. At the sides, the suspension is able to flow passed the plunger from the line 3 to the line 5. When the plunger is pulled back by an electromagnet, it exposes the opening so that the suspension can reach the carrier 11. The suspension is pumped out of the container 6 by means of the pump 9 into the storage container 2. To ensure that the suspension in the storage container 2 is always at the same level, there is a connecting line 10 between these two storage containers, through which suspension can flow from storage container 2 into storage container 6 when the liquid level is higher than the entry port of this connecting line. The cross-section of the lines 3 and 10 is made so small that the volume flow of suspension flowing through the two lines is less than the volume flow delivered by the pump 9. In the storage containers 2 and 6 are stirrers which keep the particles constantly suspended. For uniform metering, the magnetic valve 4 is controlled by an electronic timer. Details of the valve are illustrated in Figure 2.

Example of the application of the pharmaceutical composition as a suspension:

A suspension of micronised fenoterol (proportion of fenoterol: 10 percent by weight) in dichloromethane with the addition of (0.1 percent by weight) lecithin was applied to velvet with a fibre length of 1.2 mm over the basic fabric, dropwise at spacings of about 10 mm and then dried. The powder was then activated by running an edge over it and blown out of the carrier with a gentle jet of compressed air.

The inhalable portion of the particles (particle diameter < 5.8 μm) was 41.4% of the dosage expelled.

A relatively small amount of gas, e.g. 10 cc of air, forced through a 0.5 mm diameter nozzle, is sufficient to disperse (blow out) the powder.

The gas jet required for dispersal can be produced in various ways, e.g. using a cylinder provided with a nozzle out of which air is forced by a spring-operated piston, or by means of conventional small CO₂ containers which can be used to generate pressure. Instead of a cylinder with a piston it is also possible to use bellows.

A simple device in which carriers charged according to the invention can be used is diagrammatically shown in Figures 3 and 4. The main constituents are two bobbins, one of which receives the charged strip whilst the other receives the used strip. The strip is guided over a panel, whilst being guided passed an edge to activate the powder. Here, the jet of gas or air makes contact with the strip and carries the powder along. The jet is generally released at a time when air is being breathed in through the mouthpiece. It is advisable to actuate the stream of gas or air by means of the air breathed in so as to coordinate the dispersal

of the powder with the inhalation of the process.

Figure 3 shows an inhalation device viewed from in front. The carrier strip 12 with the powder, which is applied in individual dots at regular intervals on the strip, is unwound from the bobbin 13 and, once empty, wound onto the bobbin 14. By means of a transporting mechanism constructed in conventional manner, the strip is wound on, on each actuation of the device, by an amount such that a new spot arrives on the flat surface 15. The flat surface 15 is located in a mouthpiece 16 through which the patient breathes in. The slot through which the carrier strip 12 is guided into the mouthpiece is somewhat narrower than the thickness of the carrier strip 12. The upper boundary of the slot is constructed as an edge for activating the powder. Air is passed onto the dot of powder through a nozzle from a cylinder 17 in which there is a piston subjected to spring pressure with a handle 18. The spring which urges the piston towards the flat surface 15 is biased by pulling the handle 18. The dispersing step is prepared by means of a locking mechanism 19 which can be released by pressing the knob 20. Whilst breathing in through the mouthpiece 16 the patient presses the knob 20 and thus ensures that the piston propels the quantity of air contained in the cylinder through the nozzle onto the dot of powder, so that the powder is dispersed in the air breathed in.

Figure 4 diagrammatically shows the apparatus from the side, the mouthpiece 16 being shown in section. The nozzle 21 guides the jet of air out of the cylinder 17 onto the dot of powder.

The bobbins with the carrier are in this case contained in a cassette similar to that used in cassette recorders. Their movement is advantageously coupled with the movement of the handle 18, so that, each time the piston is put under tension, the carrying strip is moved on until the next dot reaches the flat surface 15.

Instead of the cylinder and spring it is also possible to use a bellows or a CO₂ cartridge of conventional construction which releases a few cc of CO₂ every time the device is used, in order to generate a gas current, as mentioned above. The CO₂ is then again guided through a nozzle onto the carrier surface coated with powder. The volume of gas needed to disperse a quantity of powder required for therapeutic purposes is generally 3 to 20 cc (under normal conditions).

Nozzles are used which have a mouth shaped to suit the type of carrier. In the case of circular dots of powder, the nozzle has a small, preferably circular aperture. In the case of larger, powder-coated carrier surfaces, a slot-shaped or rectangular nozzle may be more appropriate. In this case, a larger quantity of gas is used, if necessary, in order to ensure the required speed of outflow.

The accuracy of metering was measured in a series of tests in which either (tests 1, 2, 3) a carrier strip was continuously coated by the application of dry powder and a sharply defined section of the strip was investigated in each case or else a strip was used in which only certain places had a coating of powder.

The following surface coatings and relative standard deviations were found:

Material	Surface covering	Relative standard deviation
1. Velour-film	6.6 mg/cm ²	6.3%
2. Velvet	2.2 mg/cm ²	6.0%
3. Niki	5.4 mg/cm ²	6.2%
4. Velour-film with individual circular dots of powder*	2.1 mg/dot	11.2%

* When the powder was applied the carrier was covered with a perforated film. The perforations were 4 mm in diameter and spaced 10 to 15 mm apart. By improving the charge, the standard deviation could be reduced still further in subsequent tests.

For virtually complete dispersal on blowing out the powder, a relatively small amount of gas is sufficient, e.g. 10 cc of air which is forced through a 0.8 mm diameter nozzle (in the case of the dots of powder according to test number 4). Excellent break-up is found.

As was established by means of the Andersen impactor using micronised fenoterol, 40% of the particles of the dosage expelled were in the particle size range below 5.8 μm .

Claims

1. Carrier (11) charged with powdered pharmaceutical preparation for the production of aerosols for inhalation, characterised in that it consists of a substantially flat material on which fibres are arranged in a velvet- or velour-like manner and the powder is incorporated between the fibres.
2. Powder-charged carrier according to claim 1, characterised in that the fibre length is 0.1 to 3 mm.
3. Powder-charged carrier according to claim 1 or 2, characterised in that the layer which carries the fibres is flexible.
4. Powder-charged carrier according to claim 1 or 2, characterised in that the layer which carries the fibres is rigid.
5. Powder-charged carrier according to one of claims 1 to 4, characterised in that the entire carrier surface is uniformly charged with powder.
6. Powder-charged carrier according to one of claims 1 to 4, characterised in that only partial areas of the carrier are charged with powder, the individual charged partial areas of the carrier each containing a single dose of a pharmaceutical substance.
7. Powder-charged carrier according to one of claims 1 to 6, characterised in that the carrier is provided with a protective film on the powder-charged side or on both sides.
8. Process for metering powders for inhalation, characterised in that, by means of a gas jet, a defined



amount of powder is blown out from a carrier according to one of claims 1 to 7 and dispersed in the air breathed in.

9. Process according to claim 8, characterised in that the area of the carrier from which the powder is to be blown out is defined by a mask.

10. Process for producing a carrier according to one of claims 1 to 7, characterised in that the powder is uniformly distributed on the carrier and is incorporated in the fibre layer in one or more steps using a doctor blade.

11. Process for producing a carrier according to one of claims 1 to 7, characterised in that the powder is applied to the velvet- or velour-like carrier in the form of a small amount of a suspension and the suspending agent is evaporated off.

12. Process for metering powders for inhalation, characterised in that single doses of the powder are applied to a carrier according to one of claims 1 to 7 in the form of a suspension, then activated after drying, blown out of the carrier by means of a gas jet and dispersed in the air breathed in.

