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(54) DISODIUM CROMOGLYCATE PELLETS OR GRANULES

(71) We, FISONS LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London W1X 0AH, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a new form of disodium cromoglycate.

In our British Patent No. 1,122,284 we have described and claimed in insufflator device for use in the administration of powdered medicaments by inhalation comprising a propeller-like device carrying a powder capsule rotatably mounted within a tubular housing by means of a shaft loosely journalled in a tapered bearing tube, the housing having a mouthpiece whereby a user can inhale air through the device. With that device, and other devices, e.g. that described in British Patent Specification No. 1,331,216, a user inhales air through the device which causes a powder container mounted therein to rotate. Powder within the container is fluidised and dispensed into the air stream which is inhaled by the user. For optimum dispensing it has been found that the powdered medicament particles should be comparatively free-flowing, but fine disodium cromoglycate powders are not sufficiently free-flowing.

We have now found that this problem can be mitigated or overcome by forming powdered disodium cromoglycate into small pellets or granules which are of low bulk density. The formation of the disodium cromoglycate into pellets or granules also aids the filling of the disodium cromoglycate into capsules or other containers and can enable diluents such as coarse lactose, which have in the past been incorporated into powder inhalation compositions, to be omitted from the composition.

Accordingly the present invention provides disodium cromoglycate in pellet or granule form and having a loose bulk density of less than 0.3g per cc, preferably from 0.2 to 0.3g per cc, and most preferably from 0.22 to 0.28 g per cc. The pellets or granules are preferably from 10 to 1,000, preferably 30 to 500, microns in diameter and comprise an agglomeration of individual medicament particles, at least 90% and preferably at least 95% by weight of which have a diameter of less than 10 microns.

The pellets or granules are preferably pellets or granules described in our co-pending Application No. 2606/76 (Serial No. 1,569,611).

The pellet or granule preferably has an internal coherence such that the pellet or granule remains intact when filled into a container, e.g. a capsule, using automatic or semi-automatic filling machines, under conditions of transport and storage, and when fluidised within a container in the device from which it is intended to dispense the pellets or granules and yet may be broken up into particles of a therapeutically effective size outside the container as it discharges from the container. It is preferred that the disodium cromoglycate has greater than 95% by weight of the particles, of less than 10 microns, e.g. from 0.01 to 10, and preferably from 1 to 4, microns diameter, before incorporation into the pellets or granules of the invention.

The pellets or granules may contain other ingredients, e.g. diluents colouring and flavouring agents.

A small proportion of water, which, if necessary, is added to the disodium cromoglycate in the vapour phase for pellets and in the liquid phase for granules is usually sufficient to act as binder. We prefer the pellets or granules to contain less than 15% and preferably from 8 to 11% by weight of water.

As a general guide, we have found that satisfactory pellets or granules for use in insufflators of the type described in British Patent No. 1.122.284 (commercially available under the Registered Trade Mark 'Spin-haler') and powered by human inhalation have a mean size in the range of

from 50 to 250 microns, preferably a mean size in the range 120 to 160 microns and most preferably a mean size of about 140 microns.

The pellets or granules should be sufficiently coherent to be filled into containers, transported and stored, since appreciable break-up of the pellets or granules should not occur under these conditions.

The pellets and granules according to the invention have a lower loose bulk density than granules or pellets made by conventional techniques.

From another aspect the invention also provides a capsule, cartridge or like container containing pellets or granules of the invention, optionally in association with other pellets, granules or particles. We prefer the container to be loosely filled to less than about 80% by volume, preferably less than about 50% by volume, with the pellets or granules of the invention. The pellets or granules should of course not be compacted into the container. We prefer the container, e.g. capsule, to contain from 10 to 100 mg of the pellets or granules. The container may conveniently be pierced (and overcapped, e.g. with a plastic overcap) during its manufacture and then used, after removal of the overcap, in an inhalation device which has no piercing mechanism.

Where it is desired to use the pellets or granules of the invention in association with other ingredients such as colourants, sweeteners or carriers such as lactose, these other ingredients may be applied, to or admixed with the pellets or granules using conventional techniques. We prefer the pellets or granules of the invention to contain disodium cromoglycate and water only and not to be mixed with any other ingredients.

The pellets or granules of the invention may be made by a number of methods.

Thus pellets or granules according to the invention may be made by a method which comprises subjecting particles of disodium cromoglycate (optionally in admixture with any other ingredient it is desired to incorporate into the pellets) which either are intrinsically, or have been rendered, self-agglomerative to a controlled agglomeration. This controlled agglomeration may be carried out by,

(a) extruding the particles of sodium cromoglycate through an aperture,
(b) controlled agglomeration in a fluidised bed, or
(c) spray drying a solution or slurry of the disodium cromoglycate.

In method (a) which is the preferred method, finely divided disodium cromoglycate, e.g. having a mean particle size in the range 0.01 to 10 microns may, if necessary, be subjected to an initial treatment to cause the powder particles to be self-agglomerative. Thus the treatment may be carried out by exposing the powder particles to water.

When pellets are required the powder particles may be subjected to a humid atmosphere, for example at a temperature of from about 15° to 50°C. It will not usually be necessary to increase the water content of the powder beyond about 15% by weight, e.g. to from 5 to 10% when pellets are required. After the particles have been rendered self-agglomerative, they are passed (optionally after being rolled in for example a drum or pan for a controlled time) through an aperture of approximately the size of the desired pellets, e.g. they are forced through the apertures of a vibrating sieve which is of similar mesh aperture to the desired final pellet or granule size. The product of this passage through an aperture are shaped pre-pellets of the disodium cromoglycate.

When granules are required the powder particles may be mixed with an excess of a suitable solvent, e.g. liquid water, and the moistened material passed through an aperture, e.g. a sieve such as a vibrating sieve, of approximately equal to or larger than the mesh size required in the final granules and then drying the resulting sieved material to the desired final solvent, e.g. water, content. The material may then be dry granulated to give the required product.

When it is desired to incorporate another ingredient, e.g. a binder, into the soft granules the other ingredient may conveniently either be mixed with the disodium cromoglycate before it is moistened or may be incorporated in the solvent used to moisten the disodium cromoglycate.

The amount of water, or other solvent, used in the granulation can, under certain circumstances, be critical. Thus we have found that use of greater than about 25% by weight of water may cause the granules to be too strong and dense. We thus prefer to use disodium cromoglycate containing from about 12 to 25%, and more preferably from 17 to 23% by weight of water.

The drying is preferably effected in a preheated forced convection hot air oven. The temperature of drying is desirably from 60 to 100°C, and more especially from 80 to 90°C.

The granules may also be made by controlled agglomeration of the disodium cromoglycate in a fluidised bed or by spray drying a solution or slurry of the disodium cromoglycate.

In process (b) the fine particles of disodium cromoglycate to be formed into pellets or granules may be suspended, together with any other ingredients it is desired to

incorporate in the pellets or granules, in a gas stream in a fluidised bed apparatus. The water content of the solid material may be adjusted by variation of the humidity of the gas stream passing through the fluidised bed or by spraying water into the bed. The disodium cromoglycate may be treated in the fluidised bed for a time and under conditions sufficient to produce pre-pellets or granules of the desired density and size.

In process (c) a solution or more preferably a slurry, of the disodium cromoglycate may be spray dried to produce a granule. We prefer to use a slurry of discrete disodium cromoglycate particles of the desired fine particle size, the slurry also containing any other ingredients it is desired to incorporate in the granules. The liquid in the slurry is preferably a non-solvent or a poor solvent for the disodium cromoglycate so that no, or not many, disodium cromoglycate bridges are formed between the disodium cromoglycate particles during the spray drying. When a controlled amount of water is desired in the product a correspondingly greater amount of water may be included in the liquid in the slurry.

The extent of compaction of the treated powder during the controlled agglomeration will vary according to the method and powder used in the agglomeration. However, as a guide, we have found that suitable pre-pellets may be formed by process (a) from a powder of disodium cromoglycate containing from about 8 to 10% by weight of water, by forcing the powder through a sieve having apertures of about 150 micron size.

The pre-pellets produced by any of the above processes may, if desired or necessary be subjected to tumbling and agitation using conventional methods until the desired size, shape and coherence of the pellets are achieved. We prefer a proportion e.g. a majority, of the soft pellets to be approximately spherical. Conveniently the tumbling and agitation are carried out in a pan or drum type of pelletising machine. The treatment of the pre-pellets in such a machine is carried out until the majority of pellets in the charge have a size within the desired range. The size of the pre-pellets used and the conditions used in their agitation and tumbling may be varied in known manner to achieve the desired final size of pellet. The time for which the pellets are tumbled is, in certain circumstances, of importance to the production of viable pellets. The effect of the tumbling and agitation of the pellets is in general to strengthen them and increase their size slightly and to make them more nearly spherical in shape.

As indicated above the final product which issues from the agitation or tumbling step will have a range of sizes about the desired mean size. The produce may be classified, e.g. sieved, to remove over and under sized material. The over and under sized materially may be broken down into very fine particles and recycled to the agglomeration stage if desired.

The soft pellets or granules may be put up in any suitable form of container such as a capsule or cartridge. Where it is desired to use the pellets or granules of the invention in association with other ingredients such as colourants, sweeteners or carriers such as lactose, these other ingredients may be applied to or admixed with the pellets or granules using conventional techniques. We prefer the pellets or granules of the invention to contain sodium cromoglycate and water only.

In this specification the term 'pellet' is used to denote an agglomeration which is held together by interparticulate (e.g. Van der Waal's) forces and is typically made by a process involving water vapour. Pellets are in general spherical in shape. Granules are typically made by overwetting the medicament with solvent, e.g. water, and then removing some of the solvent.

Medicaments in pellet or granular form, wherein the pellet or granule is soft, is from 10 to 1,000 microns in diameter, comprises an agglomerization of fine medicament particles and are characterised by a variety of parameters are described and claimed in our co-pending Applications Nos. 2606/76 (Serial No. 1,569,611) and 2608/76. Particulate disodium cromoglycate containing 12 to 25% by weight of water is described and claimed in our copending Application No. 5574/78 (Serial No. 1,569,613).

The invention will now be illustrated by the following Examples in which all parts and percentages are by weight unless otherwise stated.

EXAMPLE 1

The moisture content of finely ground disodium cromoglycate having at least 98% thereof of particle size less than 10 microns and having a mass median diameter of from 1 to 3 microns was adjusted from an initial value of from 4 to 6% by weight to a value of about 9.5% by weight by exposure of the powder on a tray in an atmosphere of relative humidity 33% at 18 to 24°C.

After the desired moisture content had been achieved, the treated powder was (after an optional initial rolling in a drum pelletiser) tipped onto a 150 micron aperture stainless steel sieve screen mounted in a Russel vibratory sifter operating at a frequency of 1,000 cycles per second. The powder on the screen was forced through the sieve apertures using a stainless steel spatula pushed across the surface of the screen. The material issuing from the sifter

as particles with a mean particle diameter of about 150 microns was fed directly to a drum pelletiser adapted to rotate about a horizontal axis. The drum of the pelletiser was approximately 0.3m in internal diameter and 0.37m long with one end closed and the other end provided with a frusto conical shoulder leading to a 0.18m orifice through which material could be charged to or removed from the drum. The interior of the drum was highly polished. Two kilograms of the material from the sifter were loaded into the drum which was then rotated at a peripheral speed of 0.38m per second ± 0.025m per second for 15 minutes. At the end of this time the soft pellets had a mean particle diameter of 135 microns and not more than 10% by weight was retained on a 350 micron aperture sieve and not less than 90% by weight was retained on a 63 micron aperture sieve. The moisture content of the final soft pellets was in the range 8.5 to 10.5% by weight.

It will be appreciated that those steps of the process carried out after adjustment of the moisture content of the initial powder should be carried out under conditions of controlled humidity so as not to alter the water content of the powder appreciably. The water used in the process should be sterile and the air used in the process should be Class 100 air.

The soft pellets produced by the above procedure are approximately spherical, and have an open and loose structure and a fluffy surface when viewed under a microscope.

Up to 90 mg, e.g. 40 to 60 mg, of the above soft pellets were placed in a gelatine capsule having two holes 0.8 mm in diameter pierced in the should thereof which was mounted in a device as described in British Patent No. 1,122,284 having the detailed construction and dimensions referred to above. When air at a flow rate of 60 litres per minute was passed through this device, it was found that the charge in the capsule was consistently completely dispensed into the airstream and broken up to provide a cloud of very fine particles suitable for inhalation.

By way of contrast, when the initial finely ground powder from which the pellets had been prepared was tested under identical conditions, comparatively little of the powder was dispensed from test to test.

EXAMPLE 2

1,000g of finely ground disodium cromoglycate of determined water content was placed in the bowl of a planetary mixer. The calculated amount of water to bring the moisture content of the disodium cromoglycate to within the desired range was then added gradually, the sides of the mixer bowl being scraped regularly to ensure even moisture distribution. The damp disodium cromoglycate was then passed through a vibrating sieve having a mesh size of 1,000 microns. The product was then dried in a preheated forced convection hot air oven at 85°C for 2 hours until the moisture content of the granules was in the range 5 to 8% by weight. The granules were then sieved through a 250 micron screen. The resulting granulse were found to flow well and could be filled easily into gelatin capsules.

WHAT WE CLAIM IS:—

1. Pellets or granules comprising sodium cromoglycate and having a loose bulk density of less than 0.3g per cc.
2. Pellets or granules according to Claim 1 having a loose bulk density of from 0.2 to 0.3g per cc.
3. Pellets or granules according to Claim 2 having a loose bulk density of from 0.22 to 0.28g per cc.
4. Pellets or granules according to any one of the preceding claims, wherein the pellets or granules are from 10 to 1,000 microns in diameter and comprise an agglomeration of individual medicament particles at least 90% of which have a diameter of less than 10 microns.
5. Pellets or granules according to any one of the preceding claims, which are from 30 to 500 microns in diameter.
6. Pellets or granules according to Claim 5, which are of mean size of from 50 to 250 microns.
7. Pellets or granules according to Claim 6, wherein the mean size is from 120 to 160 microns.
8. Pellets or granules according to Claim 7, wherein the mean size is 140 microns.
9. Pellets or granules according to any one of claims 4 to 8, wherein at least 95% by weight of the disodium cromoglycate particles have a diameter of less than 10 microns.
10. Pellets or granules according to Claim 9, wherein at least 95% by weight of the disodium cromoglycate particles have a diameter of from 0.01 to 10 microns.
11. Pellets or granules according to Claim 9, wherein at least 95% by weight of the disodium cromoglycate particles have a diameter of from 1 to 4 microns.
12. Pellets or granules according to any

one of the preceding claims, comprising less than 15% by weight of water.

13. Pellets or granules according to Claim 12, comprising from 5 to 10% by weight of water.

14. Pellets or granules according to any one of the preceding claims, wherein the pellet is spherical.

15. A container containing pellets or granules according to any one of the preceding claims.

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Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to patents No. 1,520,248, 1,410,588 and 1,242,212.

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