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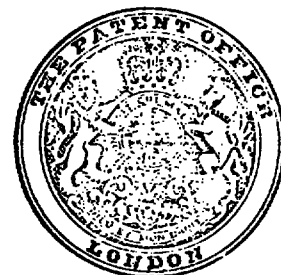
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(54) DRUG FOR USE IN PHARMACEUTICAL COMPOSITION

(71) We, Fisons Pharmaceuticals Limited, a British Company, of 12 Derby Road, Loughborough, Leicestershire, 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 an improved form of drug, suitable for use in pharmaceutical compositions for oral inhalation. More particularly the invention is concerned with a form of drug suitable for use in pharmaceutical compositions which are to be dispersed into an air stream by a fluidisation technique which uses the inspiratory action of the inhaler as the principal source of energy. The fluidisation technique is that achieved when powder within a container is subjected to simultaneous rotation and vibration. Such fluidisation is achieved in the dispenser described in French Patent No. 1471722 which corresponds to British Patent Specification No. 1,122,284. An example of such a form of device is one which comprises a hollow elongate housing having at both ends thereof one or more passageways adapted to permit the passage of air and having one end thereof adapted for insertion into the mouth and a propeller-like device rotatably mounted in the said housing on a rigid shaft mounted in said housing and co-axial with the longitudinal axis of the housing; said propeller-like device having, on the part thereof furthest from the end of the housing adapted for insertion into the mouth, mounting means adapted to receive a container, such as a gelatine capsule for the medicament to be inhaled.

Medicaments for administration by inhalation should be of a controlled particle size in order to achieve maximum penetration into the lungs.

According to the invention therefore we pro-

vide sodium chromoglycate having an effective particle size, as hereinafter defined, of from 0.01 to 10 and preferably 1 to 10 microns.

Powders in this particle size range are not readily fluidised by the above technique because of cohesive forces between the individual particles, but it has now been found that such particles may be rendered readily fluidisable using such fluidising techniques by mixing the finely divided sodium chromoglycate with a coarser carrier medium whose particles have sizes falling within a given range.

The pharmaceutical powder composition, which is described and claimed in our co-pending application No. 36270/67 (serial No. 1,242,211), comprises a mixture of sodium chromoglycate having an effective particle size, as hereinafter defined, in the range of 0.01 to 10 microns and a solid pharmaceutically acceptable water soluble carrier having an effective particle size, as hereinafter defined, in the range of from 30 to 80 microns.

For the purpose of the present invention there is no distinction between a single particle of given size and an agglomerate of the same size which is composed of finer individual particles. The term "effective particle size" is therefore used herein and in the claims, where the context permits, to denote the apparent particle size of a body without distinction as to the number of individual particles which go to make up that body. The effective particle sizes quoted herein are those as measured with a Coulter counter.

In measuring particle sizes with a Coulter counter, the sample to be analysed is dispersed in an electrolyte into which dips a glass tube. The glass tube has a hole through the wall thereof with electrodes mounted on either side of the hole in the tube wall. The tube is immersed sufficiently for the hole and electrodes to be submerged in the liquid. The suspension is made to flow through the hole in the glass

5 tube and as each particle passes through the orifice it displaces its own volume of electrolyte, thus changing the resistance across the hole. This change in resistance is converted into a voltage pulse with an amplitude proportional to the particle volume. The pulses are fed to an electronic counter with an adjustable threshold level such that all pulses above the threshold are counted. By setting the threshold level at different values it is possible to determine the number of particles falling within given size ranges and thus the proportion of particles in a sample which fall outside a desired particle size range.

15 Suitably at least 50% by weight of the sodium chromoglycate is in the effective particles size range 2—6 microns. Sodium chromoglycate is the di-sodium salt of 1,3-bis(2-carboxy-chromon-5-yloxy)-propan-2-ol and is described and claimed in Patent Specification No. 1,144,905 published 12th March 1969.

20 The finely divided sodium chromoglycate may be prepared by direct milling down to the desired particle size range.

25 The compositions will generally be put up in gelatine, plastic or other capsules.

There is also provided, therefore, as a further feature of the invention, a dosage unit comprising a capsule containing sodium chromoglycate having an effective particle size in the range of from 0.01 to 10 microns.

30 In order that the invention may be well understood, the following Examples are given by way of illustration only:

35 EXAMPLE 1

Commercially available ground crystalline lactose having an effective particle size of from 1 to 100 microns (less than 30% by weight greater than 60 microns, not more than 30% by weight less than 30 microns) was passed through an air classifier, set to remove material having an effective particle size of less than 30 microns. The product from the air classifier contained less than 4% by weight of material of less than 32 microns effective size. This product was then sieved through a sieve having a mesh aperture of 63 microns to produce a lactose product which contained less than 10% by weight of particles with an effective size less than 32 microns and less than 20% by weight with an effective particle size in excess of 62 microns as determined on an Alpine air jet sieve.

55 The sodium chromoglycate was passed through a fluid energy mill in an air stream until the product contained at least 50% by weight of particles in the effective size range

2—6 microns as determined on a Coulter counter.

Compositions containing the desired proportions of the coarse and fine materials were mixed together in a planetary mixer and the mixture then passed through a 30 mesh sieve (British Standard) to remove or break up agglomerated particles.

The compositions were then put up in gelatine capsules containing about 40 mg of the composition (capsule approximately $\frac{1}{3}$ full) and the ease of emptying of the composition from the capsule determined. The ease of emptying was assessed by mounting a pierced capsule in the capsule holder of the powder insufflator of French Patent Specification No. 1471722, which corresponds to British Patent Specification No. 1,122,284. The insufflator was then mounted in a hole in the side wall of a chamber connected to a bellows. The bellows were designed to suck air through the chamber, and hence the insufflator acting as the air inlet thereto, at a rate of 1 litre per second. Each suck of the bellows lasted one second.

The capsule was weighed prior to mounting in the insufflator. The bellows were then operated to give seven one second sucks and the capsule reweighed to determine the amount of powder removed from the capsule. The amount of powder removed is related to the ease of fluidisation of the powder.

The compositions prepared and tested are set out in Table 1. By way of comparison a composition containing no coarse diluent was prepared and tested in each case. Those compositions containing the coarse carrier were all found to empty from the capsule at a satisfactory rate, in general from 85—90% of the composition, whereas in the absence of the coarse diluent the emptying rates were much lower, about 15% or less, and were unpredictable.

EXAMPLE 2

By way of comparison a further series of compositions were prepared which contained coarse carrier material which possessed an appreciable proportion of particles with an effective size outside the range 30—80 microns. The emptying rates for these compositions are set out in Table 2.

From these results it will be seen that the rate of emptying of a capsule, containing a composition which comprises an appreciable proportion of particles whose effective size fell outside the range 30—80 microns, was very low and unpredictable, thus rendering the administration of such compositions by inhalation unsatisfactory.

TABLE 1

Fine material: nature of material and effective particle size	Parts by weight used	Coarse carrier: nature of material and effective particle size	Parts by weight used
Sodium chromoglycate (1—10m, at least 50% w/w in the range 2—6m)	20	Crystalline lactose (32—63m)	19.9
Isoprenaline sulphate (1—10m, at least 50% w/w in the range 2—6m)	0.1		

TABLE 2

Effective particle size in microns of sodium chromoglycate	Parts by weight used	Nature of coarse material	Effective particle size in microns	Parts by weight used	% w/w of material removed from capsule
1—10, at least 50% w/w 2—6	20	Crystalline lactose	32—63	20	87.2
"	10	"	Less than 30	30	0*
"	30	"	"	10	10*
"	20	"	"	20	0*
"	0	"	1—100	40	Totally unpredictable
"	20	"	10—30	20	20*
"	20	"	10—63	20	58.6

In the above Table the results marked * are unpredictable and many results were at total variance with any general trend which could be assessed. The results of these tests are therefore given as the general trend and not as a mean of the various results obtained.

WHAT WE CLAIM IS:—

1. Sodium chromoglycate having an effective particle size, as hereinbefore defined, of from 0.01 to 10 microns.
- 5 2. Sodium chromoglycate having an effective particle size, as hereinbefore defined, of from 1 to 10 microns.
3. Sodium chromoglycate according to either Claim 1 or Claim 2, wherein at least
- 10 50% by weight of the sodium chromoglycate is in the effective particle size range of 2 to 6 microns.
4. A capsule containing sodium chromoglycate having an effective particle size, as herein-

before defined, in the range 0.01 to 10 microns. 15

5. A capsule according to Claim 5 containing from 10 to 30 mg of sodium chromoglycate.

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