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(54) Title: FLUID ENERGY MILLING PROCESS AND APPARATUS

(57) Abstract

A fluid energy milling apparatus including means for adjusting humidity of the compressed air used for milling provides improved micronised product, in particular hydrates for use as drug substance in pharmaceutical compositions.

FUID ENERGY MILLING PROCESS AND APPARATUS

This invention is concerned with a process and apparatus for producing finely divided powders, especially of drug substances. In particular, the present invention relates to improvements in fluid energy milling.

Fluid energy milling, also known as micronising, is a procedure commonly used for producing finely divided powders. It is especially suitable for drug substances because there are no grinding media to contaminate the product. The reduction in particle size in the fluid energy mill is caused by attrition between the particles of the substance being milled, using energy imparted by compressed air.

The compressed air used in fluid energy milling has a very low humidity because of the increased potential for condensation in compressed air systems. Moisture is removed from the air after compression to avoid problems with condensation in apparatus in which the compressed air is used. It is customary to remove moisture by condensation, by cooling the compressed air after compression, and then to pass the compressed air through a desiccant tower before it is fed into a fluid energy mill.
Typically, the compressed air used in fluid energy milling has a pressure of around 6 bar and will have a dew point (at atmospheric pressure) below -40 °C, and which may be as low as -70 °C.

The process of micronisation may disrupt the crystal structure of substances being processed due to attrition during the milling. When milling crystalline hydrates and solvates the combination of attrition and very dry air may cause additional damage, by stripping water/solvate molecules from the crystal structure during processing. After milling the micronised material may be able to re-attain its original crystal structure over a period of time, depending on storage conditions. Therefore, a drug substance which is a crystalline hydrate may possibly not be at its original specification after fluid energy milling and may return to its original specification only after an unpredictable length of time in storage. In addition, the damage caused by attrition/desolvation may affect the intended properties of the product, for example, surface energy, stability, bioavailability.

In a particular case, a milled powder agglomerated during further processing rather than dispersing uniformly.

The present invention is based on the discovery that controlling the humidity of the compressed air used in fluid energy milling in a range which is considerably higher than that generally used, but still below the humidity which would lead to condensation problems in the mill, results in less damage to the crystallinity in the milled product.The consequent reduction in or avoidance of desiccation of the substance during the milling processalso facilitates re-attainment of the original level of crystallinity after milling. Therefore, this invention provides micronised output that is more consistent and with improved control of quality attributes. This gives much reduced inter-batch variation, leading to less reworking or failure of batches. In addition, theprocess of the invention does not have a detrimental effect on the particle size reduction achieved by the micronisation process.

In its broadest aspect, the present invention provides a fluid energy milling apparatus including means for adjusting humidity of the compressed air used for milling.

The invention also provides a milling process which comprises feeding compressed air into a mill chamber containing particulate material and subjecting the material to fluid energy milling, characterised in that the humidity of the compressed air is monitored and, if necessary, the humidity is adjusted to reduce damage to the milled product.

The adjustment made in accordance with this invention will typically be to increase the humidity. However, once the optimum value has been determined, and the apparatus has been set up to produce the desired increase in humidity of the compressed air source, it may be necessary to make adjustments during milling to correct humidity levels up or down in order to retain the optimum value.

A typical fluid energy milling system comprises a source of compressed air, a desiccant tower and a mill including a milling chamber and a collection device. The collection

device may be a filter sock in the exit air stream or an expansion chamber in which the energy of the air stream is dissipated allowing milled material to settle out. The humidity of the process air in the mill may be increased by arranging that the desiccant tower is by-passed, so that the compressed air is fed directly from the source to the mill. However, the system is preferably made controllable by providing a by-pass loop around the desiccant tower and a control valve to split the air flow between the by-pass loop and the desiccant tower, and by which the relative proportions of compressed air travelling through the by-pass and the tower can be varied. By monitoring the humidity of the air entering the mill, the amounts of air passing through the by-pass and through the desiccation tower can be adjusted using the control valve so as to achieve the desired humidity in the milling chamber.

In an alternative embodiment, undried air may be mixed with the dried air at a particular compressed air outlet in order to apply the humidity adjustment only to the process air supplying a particular piece of equipment.

In a further embodiment, humidity can be adjusted by injecting water, preferably as a mist or spray, into the compressed air-lines at an upstream location which allows moisture to be dispersed throughout the air stream before it reaches the mill.

The humidity is preferably assessed by measurement of dew point. The present invention includes any process in which the humidity is adjusted so that the process air in the mill has a dew point above the dew point of the compressed air as produced. Typically the humidity is increased to a dew point (at atmospheric pressure) of from -30 °C to 5 °C preferably about -15 °C to 0 °C. Optimal values for specific materials can be determined by routine testing, varying the dew point and assessing product quality.

The humidity is typically measured by a dew-point hygrometer. The measurement may be made continuously, for example, by a sensor placed in the air stream prior to entry into the milling chamber; or intermittently, for example, by sampling the air in the air stream prior to entry into the milling chamber.

The present invention may be applied to any fluid-energy milling process, for example in a system in which an internal classifier releases particles as they reach a pre-determined size or in a system without a classifier in which product may be passed through the mill more than onceuntil all particles are within a desired size range.

An additional advantage of the present invention, in addition to its beneficial effect on the quality of the micronised output, is that it appears to improve the micronisation process itself, making maintenance of feed rate and balancing of air pressures more easy. Furthermore, the process of the invention improves the consistency and quality of micronised drug substance output demonstrated over a period of continued production.

In addition, the present invention is particularly effective for the preparation of finely divided drug substance for use in a pharmaceutical composition. Accordingly, in a further aspect, the present invention provides for a pharmaceutical composition comprising a drug substance obtainable by a process as hereinbefore described.

The invention will improve the quality of micronised output for most substances, but is of particular applicability to the micronisation of substances susceptible to crystal damage during the process. Since removal of water of crystallinity (if present) in itself can destabilise a crystal structure, potential for crystal damage during traditional micronisation processing of crystalline hydrates is a serious problem, which the invention will overcome.

In a preferred embodiment, the procedures of the present invention are used in the preparation of micronised calcium mupirocin dihydrate (EP 0 167 856-A2, Beecham Group plc). Previously, fluid energy milling of this substance has produced micronised product that forms undesirable aggregates when compounded into an ointment base. It has been postulated that this is caused by surface energy changes resulting from loss of water of crystallisation and damage to the crystal structure by milling in very dry air. Controlling the humidity of the process air to an atmospheric pressure dew point from

about -15 to about 0 °C has overcome this problem. Micronised calcium mupirocin dihydrate produced according to the procedures of this invention preferably has a moisture content of from 3.0 to 4.0, more preferably 3.4 to 3.7% and a low amorphous content, preferably 5% or less after recovery of crystallinity.

Accordingly, in a further aspect, the present invention provides for a pharmaceutical composition comprising micronised calcium mupirocin dihydrate obtainable by a process as hereinbefore described. Such compositions will benefit from containing drug substance of more consistent quality attributes, avoiding, in an ointment, for example, formation of aggregates of calcium mupirocin dihydrate.

Preferred such compositions include ointments, creams and nasal sprays, such as those described in EP 0 231 621-A2 (Beecham Group plc), EP 0 251 434-A2 (Beecham Group plc), WO 95/10999 (SmithKline Beecham Corp) and WO 98/14189 (SmithKline Beecham). A preferred composition is an ointment comprising calcium mupirocin dihydrate in a white soft paraffin base containing a glycerine ester, available as the product Bactroban Nasal, from SmithKline Beecham. A further preferred composition is a cream comprising calcium mupirocin dihydrate in a base comprising mineral oil, polyethylene glycol (1000) monocetyl ether, cetyl alcohol, stearyl alcohol, xanthan gum and water, available as the product Bactroban Cream, from SmithKline Beecham.

This invention is illustrated by the following Examples.

Example 1

A commercial scale plant for micronising calcium-mupirocin dihydrate passes compressed air through silica gel columns to a micronising mill. A loop by-passing the silica gel drying columns was installed in the process air feed to the mill. The proportion of the air by-passing the drying columns was varied using a valve, so that the humidity of the process air could be controlled.

A single batch of calcium mupirocin was taken and divided into three portions to carry out three separate micronisations performed. The first micronisation (sub-batch A) was undertaken using the processing air as routinely delivered by the plant compressor. The dew point of the air was -58 °C. Two further portions of the input material were micronised, one (sub-batch B) using air controlled to a dew point target of -10 °C, one (sub-batch C) to a dew point of 0 °C (the upper limit of humidity obtainable in this plant). Each run produced ca. 5kg of micronised product. In each case, the dew point was measured by sampling air upstream of the mill adjacent the air inlet, and assessed as the dew point at atmospheric pressure.

All three micronised sub-batches met the required particle size specifications. The outputs were then assessed for crystallinity by solution calorimetry and the moisture contents measured by Karl Fischer analysis. The sub-batch A micronised at a dew point of -58 °C showed desiccation (Moisture Content: 3.1-3.2% w/w) and an amorphous content of ca. 15% (cf. 2% in the unmicronised dihydrate). Sub-batches B & C, produced at dew points of -10 °C and 0 °C respectively, showed no desiccation (Moisture contents: 3.6% w/w) and had amorphous contents of ca. 9%. Continued monitoring of sub-batches showed that the amorphous content steadily decreased over the next few weeks for the sub-batches B & C, whereas, due to the desiccation, sub-batch A failed to recover from the crystal damage.

Sub-batches A and B were blended with an ointment base. The ointment made from sub-batch A showed large numbers of aggregates: no aggregates were found in the ointment made from sub-batch B.

Example 2

In another experiment, the effect on moisture content and crystal damage (amorphous drug content) was compared for portions of a batch of calcium mupirocin when micronised using air controlled in a dew point range of –15°C to –5°Cwith air as generally produced from the compressed air system, of dew point ca. -50°C, whilst varying other micronisation parameters to simulate stressing of the process. The portions of the batch micronised using controlled dew point air (-15°C to -5°C) gave a mean moisture content of 3.5% w/w and a mean amorphous drug content of 16.5%. The portions of the batch micronised using standard compressed air (dew point ca. -50°C) gave a mean moisture content of 2.9% w/w and a mean amorphous drug content of 38.3%. When utilising the controlled humidity process, the output drug substance was of a much more consistent quality than with the generally produced compressed air, demonstrating that the invention improves the ruggedness of the micronisation process.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Micronised calcium mupirocin dihydrate having a moisture content of from 3.0 to 4.0% and an amorphous content of 5% or less.

2. Micronised calcium mupirocin dihydrate as claimed in claim 1 having a moisture content of from 3.4 to 3.7%.

3. A milling process for preparing micronised calcium mupirocin dihydrate according to claim 1 which comprises feeding compressed air into a mill chamber containing particulate material which is calcium mupirocin dihydrate and subjecting the material to fluid energy milling, characterised in that the humidity of the compressed air is monitored and, if necessary, the humidity is adjusted to reduce damage to the milled product.

4. A process according to claim 3 in which milling is carried out in a system comprising a compressed air source, a desiccant tower, a milling chamber and a collection device.

5. A process according to claim 3 or 4 in which means for monitoring humidity is a hygrometer sensor positioned in contact with the compressed air stream.

6. A process according to claim 3 or 4 in which the means for monitoring the humidity includes means for sampling the compressed air stream upstream of the milling chamber and a hygrometer located off-line.

7. A process according to any one of claims 3 to 6 in which the means for adjusting humidity of the compressed air is an injector for introducing a water, mist or spray into the compressed air line.

8. A process according to any one of claims 3 to 7 in which a by-pass loop diverts compressed air around the desiccant tower and a control valve is provided to switch the airflow between the desiccant tower and the by-pass loop.

9. A process according to claim 8 in which the control valve is adjustable so that varying proportions of compressed air can be sent through the desiccant tower and by-pass loop.

10. A pharmaceutical composition comprising micronised calcium mupirocin dihydrate according to claim 1 dispersed in a pharmaceutically acceptable carrier.

11. Micronised calcium mupirocin dihydrate according to claim 1, substantially as hereinbefore described with reference to the Examples.

12. A milling process according to claim 3, substantially as hereinbefore described with reference to the Examples.

13. A pharmaceutical composition according to claim 10, substantially as hereinbefore described with reference to the Examples.

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