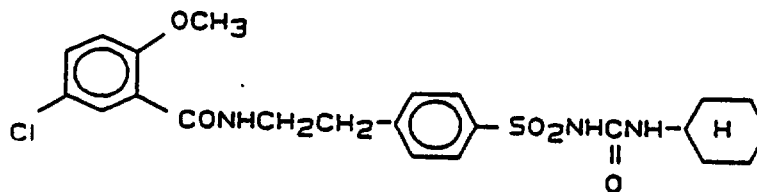


Glibenclamide, a sulfonylurea derivative of the formula



is an oral antidiabetic which is particularly suitable for the treatment of diabetes melitus (cf., for example, German Patent 1,301,812).

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It is known that, given the low solubility of glibenclamide in the digestive juices, the absorption rate depends on the degree of distribution of the active compound (German Patent 2,348,334, corresponding to US Patents 3,979,520 and 4,060,634). Very small particle sizes in the order of less than 2 μm with a surface area of at least 3 m^2/g by the BET method offer the advantage of a high absorption rate which results in a therapeutically desirable rapid drop in the blood sugar level.

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Processes for the preparation of pure glibenclamide which comprise precipitating pure glibenclamide by acidifying a solution of the potassium salt of glibenclamide are described in DE-B-214,403 and DD-A-91,647. In accordance with DD-A-204,915 pure glibenclamide is obtained by precipitating glibenclamide from a suspension of a salt mixture of the potassium salt by means of acids. The preparation of microfine glibenclamide is not described. Data regarding particle size/surface area are not given.

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Various processes are known from the literature for the preparation of glibenclamide having large surface areas in the range from 3 to 10 m^2/g by the BET method. German Patent 2,348,334 describes methods for the micro-precipitation of glibenclamide starting from glibenclamide or salts of glibenclamide.

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Microfine glibenclamide is obtained in accordance with the prior art indicated, for example by precipitating the

active compound from a water-miscible organic solvent. In this case, glibenclamide is dissolved, for example, in dimethylformamide, and the solution is run into water or water/acid mixtures with vigorous stirring. To achieve better mixing, it is proposed to run or pump the solution directly into the stirring head of an Ultra-Turrax turbine stirrer.

Alternatively, the sodium salt of glibenclamide can be dissolved in a mixture of methanol and water. After filtration, the solution is metered into water to which the amount of acid necessary for neutralization of the sodium salt has been added. To ensure good mixing, an Ultra-Turrax turbine stirrer is likewise employed.

As a further variant, the use of aqueous solutions of the alkali metal salt of glibenclamide is proposed. The low solubility of the alkali metal salts in water is disadvantageous, which means that the use of aqueous solutions for microprecipitation is not a useful industrial process.

A further way of micronizing is fine grinding of glibenclamide. In order to achieve the high surface areas of up to 10 m²/g which are desired, repeated grinding in jet mills is necessary, possibly also with addition of grinding auxiliaries.

RO Patent 89,209 (cf. Chemical Abstracts 107, 28393g (1987)) describes another variant for the preparation of microfine glibenclamide having particles of 1-2 µm. Glibenclamide is dissolved in dimethylformamide, and the solution at 80-85°C is added to initially introduced water or the water is added to the hot solution.

From various points of view, these methods representing the prior art have disadvantages in an economic respect, as far as quality is concerned, or regarding the technical complexity.

In the case of microprecipitation in accordance with the prior art using organic solvents, side reactions of glibenclamide with the solvents cannot be avoided. The permissible concentrations of byproducts in pharmaceutical active compounds such as glibenclamide are very low. In BP 80, the level of secondary compounds, such as the sulfonamide (4-[2-(5-chloro-2-methoxybenzamido)ethyl]-phenylsulfonamide) or the urethane (methyl 4-[2-(5-chloro-2-methoxybenzamido)ethyl]phenylsulfonylcarbamate) is limited at less than 0.4 %. Persons skilled in the art know that re-cleavage to form the sulfonamide occurs as a function of the temperature, in the order of some tenths of a percent even at 40° - 60°C, on dissolution of glibenclamide in dimethylformamide. If glibenclamide is dissolved in methanol, a urethane is formed, as is known, and can reach concentrations of some tenths of a percent over a period of a few hours in the temperature range from 40° - 60°C.

Since the temperatures before complete dissolution of glibenclamide in DMF, methanol or methanol/water mixtures are in the range from 40° - 60°C in the case of the concentrations which are necessary for industrial processes, a drop in the quality of glibenclamide in these precipitation processes cannot be excluded, even if very careful procedures are followed.

A further disadvantage of these precipitation processes is the additional costs incurred on disposal of the organic solvents, whether by recycling, combustion or biodegradation in the treatment plant.

The residual levels of solvents in the product is a further problem in the case of these processes for microprecipitation. Particularly high-boiling solvents such as dimethylformamide are bound adsorptively at the large surface of the product. Substantial removal, as is necessary for pharmaceutical active compounds, is possible, but very complex.

It is furthermore known to those skilled in the art that the surface areas of microprecipitated products can vary within broad limits since the crystal growth conditions are not adequately determined by the precipitation conditions. Thus, it is frequently observed that the surface area of the active compound is not within the tolerances of the specification. In such cases, it is necessary to re-work the product with high additional costs.

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Microprecipitation from solution and also fine grinding are an additional process step which requires special technical equipment.

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For fine grinding, a grinding unit, usually comprising a jet mill and a complex dust removal system, is necessary to completely remove the pharmacologically highly-effective active compound.

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Production plants for microprecipitation require special equipment in order to be able to carry out the mixing, which is preferably carried out, of the solutions in rotor-stator systems, such as the Ultra-Turrax turbine stirrer or in mixer pumps.

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Surprisingly, it has now been found that microprecipitation can be carried out in a technically very simple, economically and ecologically very favorable manner.

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The invention therefore relates to a process for the preparation of a micronized form of glibenclamide in which the active compound particles have a surface area of at least $3 \text{ m}^2/\text{g}$ by the BET method, which comprises acidifying a suspension of a sparingly-soluble salt of glibenclamide in water using an acid to give glibenclamide precipitated in microfine form, and to the micronized glibenclamide obtainable by this process.

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Special technical equipment is not necessary for the

preparation. The process according to the invention can be carried out in a standard stirred kettle.

5 A further advantage of the process according to the invention is that the surface area of the precipitated active compound can be determined in a reproducible manner by means of the precipitation temperature.

10 For example, in the preparation of the sodium salt, the surface area is a clear function of the temperature in the temperature range from 20° to 60°C. Mean surface areas of 14-15 m²/g are achieved at 20°C, and a surface area of 2.5-3.0 m²/g is achieved at 60°C. The preferably
15 desired surface area in the range from 5-10 m²/g is achieved in the temperature range from 35-45°C.

Suitable salts of glibenclamide are the salts of the alkali metals lithium, sodium or potassium and the ammonium salt, but preferably the sodium salt.

20 The mineral acids nitric acid, sulfuric acid, hydrochloric acid or phosphoric acid and the organic acids acetic acid or citric acid are suitable for the precipitation. Nitric acid or hydrochloric acid is preferably employed.
25 The pH value of the suspension after precipitation is 1.0 to 6.0, preferably 2.0 to 4.5.

By adding surface-active substances, the crystalline conversion of the glibenclamide salts into microfine
30 glibenclamide can be influenced. Wetting agents which can be employed are physiologically acceptable ionogenic and non-ionogenic substances. Polyoxyethylene stearates, such as, for example, polyoxyethylene stearate having an average of 50 ethylene oxide units, are preferred. The
35 concentration is, for example, 0.05-1.0 % by weight, preferably 0.1-0.2 % by weight, relative to the active compound.

Addition of organic, water-miscible solvents, such as,

for example, dimethylformamide or lower alcohols, to the suspensions allows the crystal size and thus the surface area of the glibenclamide to be controlled.

- 5 The glibenclamide obtainable by the process according to the invention is suitable for the preparation of medications.

10 The preparation according to the invention of micronized glibenclamide having a surface area of at least 3 m²/g, preferably 5-10 m²/g, by the BET method is explained with reference to the examples below:

Example 1

15 2480 l of demineralized water are introduced into the kettle, and 62 kg of the Na salt of glibenclamide are introduced with stirring. The temperature of the suspension is adjusted to 40°C. 65.4 l of 2N nitric acid are allowed to run in over the course of 30 minutes with
20 vigorous stirring. The glibenclamide precipitates as a finally divided suspension, which is removed by centrifugation and washed with plenty of water. After drying, the yield is 55.3 kg = 96.5 % of theory. The product has a surface area of 6.9 m²/g by the BET method. The
25 melting point is 170°C.

Example 2

1500 ml of water are introduced into the kettle. First 0.35 g of polyoxyethylene stearate 50 (®Macrogol) are
30 dissolved therein and subsequently 37.7 g of the Na salt of glibenclamide are suspended therein. The temperature of the suspension is adjusted to 30°C. 40 ml of 2N nitric acid are run in over the course of 30 minutes with vigorous stirring. The pH value of the suspension is then
35 pH 2.2. The suspension of microfine glibenclamide is filtered off with suction and carefully washed with water. After drying in vacuo at 60°C, the yield is 33.97 = 97.4% of theory. The surface area by the BET method is 8.7 m²/g.

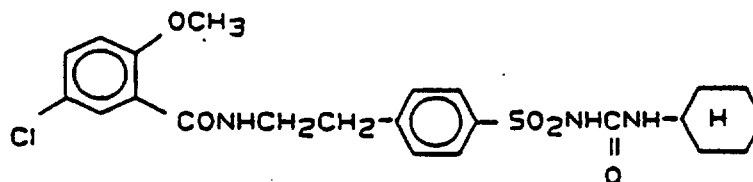
Example 3

75.5 g of the Na salt of glibenclamide are suspended in 2700 ml of demineralized water and 300 ml of methanol. 80 ml of 2N nitric acid are allowed to run in over the course of 40 minutes at 30°C with stirring. The mixture is stirred for a further 1 hour, and the product is filtered off with suction and washed with plenty of water. After drying in vacuo at 60°C, a yield of 67.8 g = 96.8 % of theory of microfine glibenclamide having a surface area of 4.8 m²/g is obtained.



Patent claims

1. A process for the preparation of a micronized form of glibenclamide of the formula



10 in which the active compound particles have a surface area of at least 3 m²/g by the BET method, which comprises acidifying a suspension of a sparingly-soluble salt of glibenclamide in water using an acid to give glibenclamide precipitated in microfine form.

- 15 2. The process as claimed in claim 1, wherein the temperature during formation of the microprecipitated glibenclamide is in the range from 5° - 90°C, preferably in the range from 30° - 50°C.

- 20 3. The process as claimed in claim 1, wherein the salt of glibenclamide employed is the lithium, calcium, ammonium or sodium salt, preferably the Na salt.

- 25 4. The process as claimed in claim 1, wherein the acid employed is a mineral acid, such as nitric acid, hydrochloric acid or sulfuric acid, or a weak organic acid, such as acetic acid or citric acid, preferably nitric acid or hydrochloric acid.

- 30 5. The process as claimed in claim 1, wherein the pH after precipitation of the micronized glibenclamide is pH 1.0-6.0, preferably pH 2.0-4.5.

- 35 6. The process as claimed in claim 1, wherein a pharmacologically acceptable wetting agent is added to the water in a concentration of from 0.05 to 1.0 % by weight, relative to the active compound.



7. The process as claimed in claim 6, wherein a polyoxyethylene stearate, preferably polyoxyethylene stearate containing an average of 50 ethylene oxide units, is added, preferably in a concentration of from 0.1 to 0.2 % by weight, relative to the active compound.
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8. The process as claimed in claim 1, wherein an organic, water-miscible solvent, such as, for example, dimethylformamide or a lower alcohol, is added to the water.
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9. The process as claimed in claim 8, wherein a mixture of water with methanol in the range from 5-30 % by volume is employed to suspend the Na salt of glibenclamide.
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