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(54) A process for preparing anhydrous lactose.

(57) Anhydrous non-hygroscopic lactose powder is prepared by conveying a hydrous lactose powder, spread on a base, continuously at normal atmospheric pressure through a heating zone, preferably at a temperature of approximately 150-200°C, the retention time being approximately 0.5-5 minutes.

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A PROCESS FOR PREPARING ANHYDROUS LACTOSE

The present invention relates to a method for continuous-working preparation of anhydrous non-hygroscopic lactose powder.

Lactose, i.e. O-β-D-galactopyranosyl - [1 → 4] - D-glycopyranose, can appear in several different physico-chemical forms. In an aqueous solution it appears in the form of two anomers, α-form and β-form, at a β/α quantity ratio of approximately 1.5/1. Lactose can be crystallized out from its aqueous solution to α-lactose monohydrate at a temperature below 93.5 ^{o}C or to β-lactose at a temperature above 93.5 ^{o}C. The crystals can be separated from the crystallized solution by several generally known methods and then dried, and thereby α-lactose monohydrate powder and β-lactose powder can be prepared. In α-lactose monohydrate the proportion of water of crystallization is 5 % of the weight of the lactose.

It is also known that the crystals need not be separated; a slurry containing crystals can be dried as such (U.S. Patent 3,639,170). Thereby a mixture of crystals and amorphous, i.e. noncrystalline lactose, formed from dissolved lactose, is obtained. If no crystallization is carried out but, instead, the aqueous solution of lactose is dried rapidly, a completely noncrystalline, i.e. amorphous, powder is obtained. According to the literature, amorphous lactose is highly hygroscopic and readily lumping.

Lactose which is purified to a high degree and fulfils the pharmacopoeia stipulations is used in the pharmaceutical industry as a filler and binder in tablets. Several studies have shown that various tableting methods set different requirements on lactose with respect to, for example, fluidity, moisture content, and anomeric balance. Anhydrous lactose powder has proved to be especially suitable in the so-called direct tableting method which is becoming increasingly common.

It is known from the literature that the water of crystallization can be driven off through treatment by a solvent, for example by boiling in methanol. However, owing to their impracticality and high cost, these methods have not been used in industrial applications.

Anhydrous lactose powder suitable for direct tableting can also be prepared by roll drum drying (U.S. Patent 3,802,914). In this process, a hot aqueous solution of lactose is dried on a rotating drum so that a powder which contains about 50 % amorphous lactose is obtained. Amorphous lactose is known to be hygroscopic and readily lumping.

It is known that by heating anhydrous lactose at a sufficiently high temperature the water of crystallization can be caused to split off, thus forming an anhydrous product. Depending on the heating method, the product obtained is either hygroscopic or non-hygroscopic (U.S. Patent 2,319,562). If the product is hygroscopic, it absorbs moisture until an amount of water corresponding to the water of crystallization which has split off has again been taken up. At the same time the powder usually lumps. One known method for preparing, by heating, a lactose powder which does not lump is extrusion (DE application 2 949 216). In this process, α-lactose monohydrate powder is extruded under pressure at a temperature above 100 ^{o}C, whereby a product which contains about 80 % lactose is obtained. However, the product obtained must be ground in order to achieve a structure suitable for tableting.

Another known process for preparing a stable, non-hygroscopic anhydrous lactose powder is two-step heating (EP application 124 928). In this process, first an unstable, hygroscopic anhydrous lactose powder is prepared by drying α-lactose monohydrate or a mixture of monohydrate and amorphous lactose in batches in a drying stove. In the second step the unstable anhydrous powder is heated further in batches so that a stable anhydrous lactose powder is formed. Such a process, comprising two separate heating steps, is in practice difficult to implement on an industrial scale.

The object of the present invention is to provide a continuous-working process by which it is possible, without separate grinding, to prepare anhydrous non-hygroscopic lactose powder which remains anhydrous even under moist conditions and which has good tableting properties. These objectives are achieved by the process according to the invention, which is characterized in that a hydrous lactose powder spread onto a base is conveyed continuously through a heating zone under normal atmospheric pressure.

What is novel and characteristic of the process according to the invention is that the heating can be carried out easily and rapidly in an uninterrupted and continuous-working step also on an industrial scale.

The anhydrous lactose powder is preferably a lactose powder which meets the pharmacopoeia stipulations. The base may be, for example, an endless, moving belt on top of which the powder is conveyed as a thin layer through the heating zone. The thickness of the powder layer is preferrably approximately 1 - 10 mm, typically approximately 2 - 5 mm. The heating can be carried out by means of heaters located above and/or under the belt; the heaters may be, for example, electric resistors, oil-filled coils, or infrared lamps. The resistors heat the belt and the air immediately above the belt so that the temperature of the air rises to approximately 150 - 200 ^{o}C, typically to approximately 175 ^{o}C. The powder is retained in the heating zone preferably for approximately 0.5 - 5 minutes, typically for about 2 - 3 minutes. During the heating the water of crystallization splits off from the powder and part of the α-form converts to β-form. After the heating, the powder is cooled with cold air to room temperature. In the process, both the heating and the cooling are carried out at normal atmospheric pressure. The powder need not be ground after the cooling but can be screened to the desired particle size. The process and the powder obtained by it are described below with the aid of examples.

Example 1

α-lactose monohydrate powder fulfilling the requirements of the USP was heated by using a continuous-working belt heater. The thickness of the powder layer was 3 mm and the temperature of the lower belt of the heater was 160 ^{o}C and of the upper belt 160 ^{o}C. The retention time of the powder in the heating zone was 5 minutes. The powder thus treated was white, readily fluid, and did not lump at a relative air humidity of 65 %. The water of crystallization of the powder split off and at the same time part of the α-form converted to β-form. The tableting properties of the powder treated by the process were substantially superior to those of untreated powder (Table 1).

TABLE 1

Effect of heating treatment on α-lactose monohydrate powder

	Untreated powder	Treated powder
Available water, % *	0.04	0.01
Water of crystallization, % **	5.53	0.51
α-lactose	97.3	78.4
β-lactose	2.7	21.6
Optical angle of roll	53.1	55.0
Absorption of moisture, % ***	-	0.12
Ultimate strength of tablet, s.c.u.	3.8	17.1

* heating-chamber heating, 2 h, 80 °C

** heating-chamber heating, 2 h, 140 °C

*** humectation at 65 % rH, 24 h

Example 2

A lactose powder fulfilling the requirements of the USP and made up of crystalline α-lactose monohydrate and an amorphous mixture of α-lactose and β-lactose was heated as a 2-mm-thick layer in a belt heater. In the heater, the temperature of the upper belt was 190 °C and of the lower belt 160 °C. The retention time of the powder in the heating zone was 3 minutes. After the heating the water of crystallization split off, and part of the α-form converted to β-form (Table 2).

TABLE 2

Effect of heating treatment on lactose powder

	Untreated powder	Treated powder
Available water, % *	0.36	0.03
Water of crystallization, % **	5.07	0.44
α-lactose, %	87.5	82.7
β-lactose, %	12.5	17.3
Optical angle of roll	52.0	54.8
Absorption of moisture, % ***	0.50	0.50
Ultimate strength of tablet, s.c.u.	15.2	19.5

* heating-chamber heating, 2 h, 80 °C

** heating-chamber heating, 2 h, 140 °C

*** humectation at 65 % rH, 24 h

CLAIMS

1. A process for preparing a substantially anhydrous non-hygroscopic lactose powder, which comprises conveying a hydrous lactose powder spread onto a base continuously, at normal atmospheric pressure, through a heating zone.

2. A process according to Claim 1, in which the lactose powder is spread on the base as a layer having a thickness of approximately 1-10 mm.

3. A process according to Claim 2 in which the layer thickness is 2-5 mm.

4. A process according to any of Claims 1 to 3, in which the lactose powder remains in the heating zone for approximately 0.5-5 minutes.

5. A process according to Claim 4 in which the lactose remains in the heating zone for 2-3 minutes.

6. A process according to any of the preceding claims, in which the temperature in the heating zone is approximately 150-200°C.

7. A process according to Claim 6 in which the said temperature is approximately 175°C.

8. A process according to any of the preceding claims, in which the hydrous lactose powder is made up primarily of α-lactose monohydrate.