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(54) Titre : PROCEDE DE PREPARATION DE COMPOSITIONS PHARMACEUTIQUES ORALES COMPRENANT DES BIPHOSPHONATES

(54) Title: PROCESS FOR THE PREPARATION OF ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING BIPHOSPHONATES

(57) Abrégé/Abstract:
The invention relates to a process for the preparation of bisphonate-containing pharmaceutical compositions for oral application, wherein the active substance is wet-granulated in manner known per se in a fluidised-bed granulator using adjuvants which have no abrasive action and wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions.

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(54) Title: PROCESS FOR THE PREPARATION OF ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING BIPHOSPHONATES

(57) Abstract

The invention relates to a process for the preparation of bisphonate–containing pharmaceutical compositions for oral application, wherein the active substance is wet–granulated in manner known per se in a fluidised–bed granulator using adjuvants which have no abrasive action and wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions.

PROCESS FOR THE PREPARATION OF ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING BIPHOSPHONATES

The invention relates to a process for the preparation of oral-application pharmaceutical compositions containing as active substance aminoalkyl-1,1-diphosphonic acid derivatives or physiologically safe salts thereof (hereinafter called by the general term bisphosphonates).

Bisphosphonates are important in the treatment of bone diseases and some disturbances of calcium metabolism such as hypercalcaemia, osteoporosis, tumour osteolysis, Paget's disease, etc.

Pharmaceutical preparations in general have to satisfy exacting requirements regarding content, uniformity of content and purity. Special properties of active substances may adversely influence the content, uniformity and purity of the form of administration. It is known that bisphosphonates are a group of substances with a strong tendency to form complexes with polyvalent metal ions. Conventional pharmaceutical preparations for oral application are usually produced in installations and apparatus with metal surfaces, and consequently when bisphosphonates are processed the highly complex-forming active substance comes into contact with complexable material. This is particularly the case when water or aqueous media are used in processing. One remedy is dry processing, particularly on the direct tableting principle, since wet granulation is avoided in that case. Direct tableting is a very suitable method for

producing high-dosage tablets. As is known, however, high-dosage forms of bisphosphonates for oral administration are particularly subject to compatibility problems, which makes oral treatment difficult. Aminodiphosphonic acids in particular cause irritation of the upper gastrointestinal tract (H. Fleisch, Bisphosphonates in Bone Disease, Herbert Fleisch, Berne, 1993; pages 126-131). In direct tableting furthermore, as in the case when non-granulated powder is filled into gelatine capsules, there is a risk of fluctuations in content, particularly for low or very low-dosage active substances. For this reason wet granulation is indispensable, in spite of the said risk of complex-forming. When high-speed mixers are used, the active substance is mixed with adjuvants and is granulated wet with water or aqueous binder solution. In the process the active substance is brought into very intensive contact with the metal surfaces of the apparatus. The risk of complex-forming can be additionally increased by the abrasive effect of some pharmaceutical adjuvants.

The object of the invention therefore is to develop a process for the preparation of bisphosphonate-containing pharmaceutical compositions for oral application, preferably containing up to 50 mg of active substance per unit dose, so as to reduce the loss of active substance in the preparation of the compositions.

To this end, according to the invention, bisphosphonates are converted by known fluidised-bed granulation (Liebermann et al. "Pharmaceutical Dosage

Forms": Tablets, 2nd Ed. 1990, Marcel Dekker, New York, Basle; Pietsch: "Size Enlargement by Agglomeration", John Wiley & Sons, Chichester) into formulations suitable for oral application. Fluidised-bed granulation is a conventional method of wet granulation. Unexpectedly, however, this method can reduce the loss of active substance or the diminution in content of active substance in the formulation to less than 6% by weight, preferably less than 4% by weight.

The invention thus relates to a process for the preparation of pharmaceutical compositions for the oral application of bisphosphonates, wherein the bisphosphonate is wet-granulated in manner known per se in a fluidised-bed granulator using adjuvants which have no abrasive action and wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions.

The said disadvantage of complex-forming during wet granulation, therefore, is no longer a problem when preparing low-dosage bisphosphonate preparations. The pharmaceutical compositions are preferably produced with a content of up to 50 mg, particularly up to 10 mg bisphosphonate per unit dose. The term "unit dose" denotes the discrete form of administration, i.e. the individual tablet or capsule.

The pharmaceutical compositions are prepared according to the invention by granulating the active substance in a fluidised-bed granulator known per se, using

adjuvants which have no abrasive effect during processing in conventional pharmaceutical production plants, e.g. as in the case of silicon dioxide.

Preferably, the active substance in solution or suspension together with an aqueous binder solution is sprayed on to other suitable adjuvants and granulated, or the active substance and adjuvants in dry powder form are placed in a fluidised-bed granulator and granulated by spraying aqueous binder solution into the powder mixture; alternatively water may also be sprayed into the powder mixture, which in this case contains a binder.

The resulting wet granulate is then dried in the fluidised-bed granulator until the material has an acceptable residual moisture content for further processing to a pharmaceutical composition in other machines. The dried granulate is passed through a screen having a suitable mesh width and then further processed by known techniques, being mixed with other additives if required.

The following bisphosphonates are active substances which can be used according to the invention in the form of free acids or pharmaceutically compatible salts or hydrates, particularly sodium salts:

(4-amino-1-hydroxybutylidene)bis-phosphonate (alendronate),

(Dichloromethylene)bis-phosphonate (clodronate),

[1-hydroxy-3-(1-pyrrolidinyl)-propylidene]bis-phosphonate (EB-1053),

(1-hydroxyethylidene)bis-phosphonate (etidronate),

[1-hydroxy-3-(methyl pentyl amino)propylidene]bis-phosphonate (ibandronate),
[Cycloheptylamino)-methylene]bis-phosphonate (incadronate),
(6-amino-1-hydroxyhexylidene)bis-phosphonate (neridronate),
[3-(dimethylamino)-1-hydroxypropylidene]bis-phosphonate (olpadronate),
(3-amino-1-hydroxypropylidene)bis-phosphonate (pamidronate),
[1-hydroxy-2-(3-pyridinyl)ethylene]bis-phosphonate (risedronate),
[[(4-chlorophenyl)thiol]-methylene]bis-phosphonate (tiludronate),
[1-hydroxy-2-imidazo-(1,2-a)pyridin-3-yl ethylidene]bis-phosphonate (YH 529),
[1-hydroxy-2-(1H-imidazol-1-yl)ethylidene]bis-phosphonate (zoledronate).

The said substances and their preparation are known and described, for example, in the following references: US Patent No. 4,705,651 (Alendronate), US Patent No. 4,927,814 (Ibandronate), US Patents Nos. 3,468,935, 3,400,147, 3,475,486 (Etidronate), O.T. Quimby et al, J. Org. Chem. 32, 4111 (1967) (Clodronate) and US Patent No. 4,505,321 (Risedronate) and US Patents Nos. 4,134,969 and 3,962,432 (Pamidronate), US Patent No. 5,130,304 (EB-1053), US Patent No. 4,970,335 (Incadronate), Belgian Patent No. 885139 (Neridronate), US Patent No. 4,054,598 (Olpadronate), US Patents Nos. 4,746,654, 4,876,248 and 4,980,171 (Tiludronate), US Patent No. 4,990,503 (YH 529) and US Patent No. 4,939,130 (Zoledronate).

The invention is preferably used for producing pharmaceutical preparations which contain the active substance in a proportion of up to 50 mg per unit dose, preferably up to 10 mg, particularly preferably 0.1 to 5 mg and 0.1 to 2.5 mg. Ibandronate is a particularly preferred active substance, particularly in the form of Na-Ibandronate monohydrate.

The adjuvants which do not have an abrasive effect during granulation may, according to the invention, be fillers such as lactose in hydrate or anhydrate form, sugar alcohols such as mannitol; tableting adjuvants such as cellulose in microcrystalline or fibrous form; and binders such as polyvinyl pyrrolidone (Povidone USP) or cellulose ethers such as methyl hydroxypropyl cellulose. At least one adjuvant is used which acts as binder.

Preferably at least one of the adjuvants is lactose, microcrystalline cellulose or polyvinyl pyrrolidone. In a preferred embodiment 1-99% by weight lactose, 1-99% by weight microcrystalline cellulose, 0.1-20% by weight are used, particularly preferably 25-75% by weight lactose, 10-20% by weight microcrystalline cellulose, and 2-3% by weight polyvinyl pyrrolidone.

The granulate is further processed by known methods, using additional adjuvants if required, into tablets, chewing tablets, effervescent tablets, film tablets, dragees and pellets or filled into hard gelatine capsules or sachets. The adjuvants used in further processing are conventional lubricants, e.g., stearic acid, disintegrants, e.g., cross-linked polyvinyl pyrrolidone (Crospovidone USPNF), flow-regulators,

e.g., colloidal silicon dioxide, tableting adjuvants etc. In one preferred embodiment the further processing of the granulate is carried out with the addition of stearic acid as lubricant in quantities of less than 5% by weight referred to the total weight of the form of administration, particularly 0.05 to 3% by weight of stearic acid.

Preparation of pharmaceutical compositions according to the invention by fluidised-bed granulation, particularly by the drying process in the fluidised-bed granulator, results in less intensive contact between the material and the surface of the apparatus, thus surprisingly reducing the loss of active substance. This is particularly advantageous when the active substance content of the unit dose is small. This substantially avoids the above-described disadvantages in the conventional production of forms for oral administration.

The invention will now be explained in further detail with reference to examples, without being limited thereto.

Example 1 (Comparative example):

Production of ibandronate 2.5 mg capsules after granulation in a high-speed mixer/granulator (batch size for 45.000 capsules).

Constituents		g
Na-Ibandronate	120.24	
Lactose		7934.76
Polyvinyl pyrrolidone		202.50
Polyvinyl pyrrolidone, cross-linked (disintegrant)		562.50
Stearic acid (lubricant)		180.00

The amount of active substance per capsule is equivalent to 2.5 mg of free acid.

Lactose, ibandronate and polyvinyl pyrrolidone were mixed for 2 minutes at a fill factor of 50% in a high-speed mixer/granulator (Diosna type) and then granulated with water for 8 minutes. The wet granulate was dried in a fluidised bed (Aeromatic-type apparatus), passed through an 0.8 mm screen, mixed with disintegrant and lubricant (Rhoenrad-type mixer, mixing time 10 minutes) and encapsulated in size-2 hard gelatine capsules without compression in a capsule machine (type MG2/G36) having a capacity of 20,000 capsules per hour.

Set weight of filling:	200.0 mg
Actual weight of filling according to in-process control:	200.9 mg

Content of active substance found in capsules produced in this way: 94.8% ± 5.2% (n = 10 individual measurements).

Example 2 (Comparative example):

Production of ibandronate 1.0 mg capsules after granulation in a high-speed mixer/granulator (batch size for 5000 capsules).

Constituents		g
Na-Ibandronate	5.345	
Lactose		999.655
Polyvinyl pyrrolidone		22.500
Polyvinyl pyrrolidone, cross-linked (disintegrant)		62.500
Stearic acid (lubricant)		10.000

The amount of active substance per capsule is equivalent to 1.0 mg of free acid.

Lactose, ibandronate and polyvinyl pyrrolidone were mixed for 2 minutes in a high-speed mixer/granulator (Diosna type) and then granulated with water for 10 minutes. The wet granulate was dried in a fluidised bed (Aeromatic-type apparatus), screened through an 0.8 mm screen, mixed with disintegrant and lubricant (Rhoenrad-type mixer, mixing time 10 minutes) and enclosed in size-2 hard gelatine capsules in a capsule machine (type KFM Harro Höfliger).

Set weight of filling:	220.00 mg
Actual weight of filling according to	

in-process control: 220.05 mg
Content of active substance found in the capsules produced in this way: 94.9% ± 1.9%
(n = 10 individual measurements)

Example 3:

Production of ibandronate 1.0 mg tablets after granulation in a fluidised bed (batch size for 60.000 tablets).

Constituents		g
Na-Ibandronate	64.14	
Lactose		4405.86
Polyvinyl pyrrolidone		150.00
Polyvinyl pyrrolidone, cross-linked (disintegrant)		300.00
Stearic acid (lubricant)		120.00
Microcrystalline cellulose		900.00
Colloidal SiO_2 (flow agent)		60.0

The amount of active substance per tablet is equivalent to 1.0 mg of free acid.

Lactose and 600 g microcrystalline cellulose were granulated with an aqueous solution of polyvinyl pyrrolidone and ibandronate in a fluidised-bed granulator (Aeromatic type). The wet granulate was dried in the fluidised bed (Aeromatic type), passed through a 1.0 mm screen, mixed with disintegrant, lubricant, flow-regulator and 300 g microcrystalline cellulose (Turbula-type mixer, mixing time 5 minutes)

and converted into tablets in a tableting press (Korsch type) having a capacity of 25,000 tablets per hour.

Set weight of tablets: 100.0 mg
Actual weight of tablets according to in-process control: 101.3 mg
Content of active substance found per tablet produced in this way: 98.3% ± 4.2% (n = 10 individual measurements).
The active substance content of the tablets was within the acceptance limits.

Example 4

Production of ibandronate 0.1 mg tablets after granulation in a fluidised bed (batch size for 150.000 tablets).

Constituents	g
Na-Ibandronate monohydrate	16.95
Lactose	11158.05
Polyvinyl pyrrolidone	375.00
Polyvinyl pyrrolidone, cross-linked (disintegrant)	750.00
Stearic acid (lubricant)	300.00
Microcrystalline cellulose	2250.00
Colloidal SiO_2 (flow agent)	150.00

The amount of active substance per tablet is equivalent to 0.1 mg of free acid.

Lactose and 1500 g microcrystalline cellulose were granulated with an aqueous solution of polyvinyl

pyrrolidone and ibandronate in a fluidised-bed granulator (Aeromatic type). The wet granulate was dried in the fluidised bed (Aeromatic type), passed through a 1.0 mm screen, mixed with disintegrant, lubricant, flow-regulator and 750 g microcrystalline cellulose (Turbula-type mixer, mixing time 10 minutes) and converted into tablets in a tableting press (Korsch type) having a capacity of 60,000 tablets per hour.

Set weight of tablets:	100.0 mg
Actual weight of tablets according to in-process control:	101.3 mg

Content of active substance found per tablet produced in this way : 98.5% ± 2.4% (n = 10 individual measurements).

The active substance content of the tablets was within the acceptance limits.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the preparation of pharmaceutical compositions for the oral application of bisphosphonates, wherein the bisphosphonate is wet-granulated in manner known per se in a fluidised-bed granulator using adjuvants which have no abrasive action, wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions containing up to 50 mg active substance per unit dose, and wherein the bisphosphonate used is alendronate, clodronate, EB-1053, etidronate, ibandronate, incadronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529 or zoledronate in the form of a free acid or a pharmaceutically compatible salt or hydrate.

2. A process according to claim 1, wherein the bisphosphonate in solution or suspension and together with an aqueous binder is sprayed on to other adjuvants and granulated.

3. A process according to claim 1, wherein the bisphosphonate and the adjuvants in dry powder form are placed in a fluidised-bed reactor and granulated by the spraying of water into the powder mixture, which in that case contains a binder, or the powder containing the active substance is granulated by the spraying in of an aqueous binder solution.

4. A process according to any of claims 1, wherein the pharmaceutically compatible salt is sodium salt.

5. A process according to claim 4, wherein the bisphosphonate used is ibandronate.

6. A process according to any of claims 1 to 5, wherein at least one of the adjuvants is: lactose, microcrystalline cellulose or polyvinyl pyrrolidone.

7. A process according to claim 6, wherein the adjuvants used are 1-99% by weight lactose, 1-99% by weight microcrystalline cellulose and 0.1-20% polyvinyl pyrrolidone.

8. A process according to claim 7, wherein 25-75% by weight lactose, 10-20% by weight microcrystalline cellulose and 2-3% by weight polyvinyl pyrrolidone are used.

9. A process according to any of claims 1 to 8, wherein further processing into tablets, capsules, film tablets, dragees, pellets, effervescent tablets, chewing tablets or granulates in sachets is carried out.

10. A process according to claim 9, wherein further processing is effected with the addition of 0.05 - 3% by weight stearic acid to the mixture.