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An agency of Industry Canada

CA 2091370 C 2005/08/02

(11)(21) 2 091 370

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1993/03/10

(41) Mise à la disp. pub./Open to Public Insp.: 1993/09/12

(45) Date de délivrance/Issue Date: 2005/08/02

(30) Priorité/Priority: 1992/03/11 (P 42 07 717.6) DE

(51) Cl.Int.^{5}/Int.Cl.^{5} A61K 31/44, A61K 31/385, A61K 9/20, A61K 9/16, A61K 31/085

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(54) Titre : COMPRIME, GRANULE ET PELLETS EN SUBSTANCES ACTIVES A TENEUR ELEVEE POUR PREPARATIONS PHARMACEUTIQUES SOLIDES TRES CONCENTREES

(54) Title: TABLETS, GRANULATES AND PELLETS WITH A HIGH ACTIVE SUBSTANCE CONTENT FOR HIGHLY CONCENTRATED, SOLID DOSAGE FORMS

(57) Abrégé/Abstract:
Solid medicinal form with an active substance (thioctic acid, mesna or flupirtine maleate) content of over 45 weight % and processes for their preparation by granulating with large amounts of water, drying and optionally conventional tableting and/or pelleting.

ABSTRACT OF THE DISCLOSURE

Solid medicinal form with an active substance (thioctic acid, mesna or flupirtine maleate) content of over 45 weight % and processes for their preparation by granulating with large amounts of water, drying and optionally conventional tableting and/or pelleting.

The present invention relates to a medicinal formulation in tablet form or granulated or in pellet form containing, for example, thioctic acid or flupirtine or mesna in granulated or pelletized form and optionally pharmaceutically acceptable auxiliary substances.

Chemically speaking, thioctic acid (alpha-lipoic acid) is an 1,2-dithiacyclopentane-3-valeric acid. The invention not only relates to the racemic form, but also to the pure (R)- or (S)-thioctic acid as well as to mixtures of (R)- and (S)-thioctic acid of any composition. Thioctic acid is a constituent of cell metabolism and is therefore found in many plants and animal organisms. It acts as one of the coenzymes in the oxidative decarboxylation of pyruvate and other alpha-ketoacids. Thioctic acid has been used for a long time in various disorders, such as in liver disorders, in liver damage due to mushroom poisoning and in diabetic and alcoholic polyneuropathy, a change in the peripheral nerves associated with metabolic disorders.

Current, commercially available thioctic acid containing tablet formulations contain a maximum of 200 mg thioctic acid in a tablet weighing 515 mg.

To simplify intake and to increase patient acceptance there is a need for thioctic acid tablets in higher concentration and smaller size.

Chemically speaking, mesna is the sodium salt of mercaptoethanesulfonic acid. Mesna is used as a mucolytic agent and to prevent bladder toxicity and nephrotoxicity in treatment involving cytostatic agents of the oxazaphosphorin type.
In addition to the sodium salt it is also possible to use the arginine salt described in EP 198 542. Flupirtine is used as the maleate to combat pain. Apart from the maleate it is also possible to use the hydrochloride, the sulphate, the mandelate as well as other pharmaceutically acceptable salts.
The proportional multiplication of the constituents in a tablet containing 200 mg thioctic acid leads, in active substance dosages of more than 500 mg per tablet, to tablets having intrinsic weights of more than 1.2 g.
Because of their size it is difficult to swallow tablets of such high intrinsic weight, which leads to their poorer acceptance.
It is necessary to reduce the proportion of active substance in the higher dosed solid medicinal form.
It is, however, impossible to manufacture thioctic acid-containing, mesna-containing or flupirtine-containing tablets with a reduced proportion of active substance of a satisfactory quality using conventional manufacturing methods.
Higher concentrations of thioctic acid lead to tablet pressing problems. The masses to be pressed tend to adhere to the pressing tools. In addition, cracks appear in the tablets parallel to their surface and in the case of biconvex tablets the domed surface (lid) tends to break away.
These faults are caused by the properties of thioctic acid, the low melting point of the substance of 60.5 °C (R, S-thioctic acid) and 47 °C (R-thioctic acid) and 46 °C (S-thioctic acid) being particularly critical.

The same problems occur when attempts are made to prepare highly concentrated mesna or flupirtine maleate tablets. Tableting faults also occur in the case of these active substances, such as adhesion and crack formation, as soon as the active substance

content in the mass to be pressed exceeds 45 weight %. Adhesion to, and smearing of, the pelleting machines are the main problems during pelleting. In addition, pellet masses moistened in conventional manner with conventional auxiliary substances display only insufficient binding of the pellets after the finished pellets have been dried.

EP-A 420 042 describes the preparation of solid medicinal forms with a high verapamil hydrochloride content through granulation with a small amount of water, the water content in relation to verapamil hydrochloride being between 2 and 10 weight %. Also in the compulsory second granulation step of the process the water content is between 2 and 10 weight %.

The present invention provides formulations with a high proportion of active substance which can easily be pressed into tablets. Accordingly, the unfavourable technical problems arising with the pressing of for example thioctic acid, mesna or flupirtine which become increasingly pronounced with increasing active substance concentration are overcome or at least mitigated.

Reduction in the proportion of auxiliary substances in the tablet simultaneously also reduces the probability of signs of intolerance, such as for example to lactose [Deutsche Apothekerzeitung 131, 1569 (1991)].

Itensive granulation of the active substances with large amounts of binding agent solutions or by granulation of an active substance / binding agent mixture with large amounts of water is provided by the invention.

In addition to these two constituents, the granulate may also contain conventional tableting auxiliary substances such as filling, disintegrating and wetting agents. The tablet may also contain additional filling, binding, disintegrating, wetting,

flow-promoting, lubricating and anti-adhesive agents apart from the granulate.

It has surprisingly been found that intensive moistening of the mass to be granulated is able to neutralize the technologically unfavourable characteristics of thioctic acid and the active substances mesna and flupirtine.

The medicinal formulations of the invention contain between 45 weight% and 100 weight% of active substance, preferably between 75 weight% and 100 weight% and, particularly preferred, between 85 weight% and 100 weight%. Related to the prepared amount of solid active substance, at least 30 weight%, preferably 40 - 100 weight%, in particular 50 - 70 weight% of water or aqueous binding agent solutions are used. Conventional granulation processes used to date operate with a maximum of 30 weight% of water (Der Pharma-Werker, Editio Cantor, 1970, page 72 - 74; Hager Handbuch der pharm. Praxis, 4th Edition 1971, Volume 7 a, page 712) as granulating liquid or solvent for the binding agent. In the case of thioctic acid a maximum of 15 weight% of water have hitherto been used as granulating liquid.

Page 86 of List, Arzneiformenlehre, Stuttgart (1985) describes the moisture content of the mass to be granulated as follows:

"It is generally found that a mass has the correct moisture content if it forms a ball when compressed in the hand and does not immediately fall apart again when released, but can be easily rubbed between the fingers without smearing". Page 158 of Voigt, Lehrbuch der pharmazeutischen Technologie, Weinheim (1987) describes the degree of moisture of the granulate as being "earth moist". Moistening agents that can be used are alcohols with 1 - 4 carbon atoms, esters of lower organic acids and lower organic alcohols with a total of up to 6 carbon atoms, for example methanol, ethanol, isopropanol, acetic acid ethyl ester and, particularly preferred, water.

Binding agents can be all pharmaceutically conventional binding agents such as cellulose derivatives (for example ethyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose), gelatin, starch, polyglycols (mean molecular mass 1000 - 35000 Dalton), polyvinyl alcohols, polyvinyl pyrrolidone, polyacrylic acid, vinyl pyrrolidone-vinyl acetate copolymerisate, alginates, saccharose or glucose, polysaccharides such as, for example natural rubbers such as, for example, gum arabic, tragacanth, pectin, guar-rubber in amounts of 1 - 30 weight%, preferably 5 - 20 weight%, in particular 10 - 15 weight%, related to active substances (concentration of the aqueous binding agent solutions 2 - 30 weight%, preferably 5 - 15 weight%).

It is also possible to simultaneously use various binding agents, for example different cellulose derivatives in association. The binding agents can be worked into the dry powder mixture or incorporated dissolved or dispersed in the granulating liquid. The combination of dry prepared and dissolved or dispersed binding agent is also suitable.

The moist mass is intensively worked mechanically in conventional manner in order to obtain even moistening and compaction of the mass. This is effected for example in a high performance granulator. These machines have a mixer arm rotating about a vertical axis and a cutter rotating at higher speed either vertically or in parallel to the mixer arm axis. (Examples of such machines are: Diosna pharma mixer, series P, Lödige ploughshare mixer FM with knife-head fittings, Colette or Fielder-mixer-granulator). Granulation occurs with maximum energy input, i.e. in each case at the highest speed of revolution of the mixer paddles and choppers and, depending on the granulator, lasts 5 - 20 minutes. The granulation consistency can be described as being pasty, but without visibly

separated liquid phase. In contradistinction thereto, when in optimum moist content, the conventional granulates are described as being of snowball-like consistency. If required, the moist mass is passed through a strainer having a ring matrix (for example Alexanderwerk-Reibschnitzler, Stephan granulating machine, Nica extruder) or a granulating sieve and further compacted in this manner. Particularly high compaction produces pellet-like products. Pellets can be defined as being spherical or cylindrical particles with a diameter of 0.1 to about 5 mm. Pellets of this kind can be rounded and flattened before drying on a rotating corrugated disc (for example in a Nica spheronizer).

The granulate or the pellets are subsequently dried in a fluidized air bed or on hurdles in the conventional manner up to a final moisture of under 10, preferably under 6 weight % and in particular under 3 weight % (related to the solid matter weight). This granulation is optionally repeated with more than 15 weight %, preferably 30 - 70 weight %, in particular 40 - 50 weight % of water or aqueous binding agent solutions in order to increase the compaction of the granulate and the binding within the granulate grains. Between moistenings, drying may be effected at a temperature of from 20 to 50°C. The binding agent content is 2 - 30 weight %, preferably 5 - 15 weight %, related to the amount of solvent used.

If necessary the granulate or the pellets are mixed with filling, binding, disintegrating, wetting, flow-promoting, lubricating and/or anti-adhesion agents. Filling agents that may for example be used are: cellulose, cellulose derivatives, saccharose, lactose, glucose, fructose, calcium phosphates, calcium sulphates, calcium carbonates, starch, modified starch, sugar alcohols such as sorbitol or mannitol.

Binding agents that are suitable are, for example, cellulose derivatives (for example ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose), gelatin, starch, modified starch, polyglycols (mean molecular mass 1000 - 35000 Dalton), polyvinyl alcohols, polyvinyl pyrrolidone, polyacrylic acid, vinyl pyrrolidone-vinyl acetate copolymerisates, alginates, saccharose, glucose, polysaccharides.
Disintegrants that may for example be used are: starch, modified starch, cellulose, cellulose derivatives, alginates or cross-linked polyvinyl pyrrolidone.

Wetting agents that may, for example, be used are: sodiumdioctyl sulfosuccinate, sodiumlauryl sulphate, polysorbates or polyoxyethylene stearic acid esters. Flow-promoting agents that may be used are, for example, colloidal silicon dioxide, talcum or magnesium stearate.
Lubricants that may, for example, be used are: magnesium stearate, calcium stearate, D,L-leucine, talcum, stearic acid, polyglycols (mean molecular mass 3000 - 35000), fatty alcohols or waxes.
Anti-adhesion agents that may, for example, be used are: starch, talcum, magnesium stearate, calcium stearate or D,L-leucine.

The mixture prepared in this way is pressed into tablets in conventional manner. In so doing it may be of advantage to reduce the temperature of the mass to be pressed to below room temperature before pressing. The temperature of the mass to be pressed can be 0 °C - 30 °C, preferably 5 °C - 20 °C, in particular 8 °C - 15 °C.

The pellets are either pressed into tablets or filled into hard gelatin capsules or bags.

The intensive mechanical processing and large amount of granulating liquid used are characterizing and decisive for the process. Precooling of the mass to be pressed (24 hours at +8 °C) further improves the pressing characteristics of the tablet mass.

Examples:

Example 1
Granulate with 300 mg thioctic acid to 318 mg granulate

Corn starch is processed to form corn starch paste in the conventional manner (List Arzneiformenlehre, Stuttgart (1985), page 88).
1500 g thioctic acid are moistened with 880 g of a 10 % aqueous corn starch paste in a Diosna P10 mixer granulator for 10 minutes (maximum energy input: mixer 433 rpm, chopper 3000 rpm). The moist mass is passed through a sieve with a 2 mm mesh size and spread on drying hurdles in a circulating air drying cabinet with an air inlet temperature of 40 °C to a relative moisture of 25 - 30 %. The dry granulate is passed through a sieve of mesh size 0.8 mm. The granulate may optionally be provided with a gastric juice-soluble, gastric juice-permeable or gastric juice-insoluble coating and filled into capsules or bags.

Example 2
Tablets with 300 mg thioctic acid to 319 mg tablet weight

1588 g of the granulate of Example 1 are mixed with 6 g magnesium stearate and pressed into biconvex tablets with a weight of 319 mg, a diameter of 10 mm and a radius of curvature of 8 mm. The tablets are smooth, shiny and without cracks. The pressing tools are free of traces of adhering tablet mass.

The tablets disintegrate within 2 minutes in the disintegration tester of DAB 9 (test liquid: water, 37 °C).

It is optionally possible to provide the tablets with a gastric juice-soluble or gastric juice-resistant film coating using conventional methods.

Example 3

Granulate with 300mg thioctic acid to 330 mg granulate

1500 g thioctic acid are mixed with 150 g hydroxypropyl cellulose. The mixture is moistened with 900 g purified water in a Diosna P10 mixer granulator for 12 minutes (maximum energy input: mixer 433 rpm, chopper level 3000 rpm).
The moist mass is passed through a granulating machine (Stephan KG-150P) with a ring cylinder, aperture size 2 mm. The moist granulate is dried in a fluidized air bed dryer (Glatt WSG 3/5) to an air inlet temperature of 30 - 40 °C at a relative moisture of 25 - 30 %. The dried granulate is passed through a sieve of mesh size 0.8 mm.
The granulate can be filled into capsules or bags.

Example 4
Tablets with 300 mg thioctic acid to 331 mg tablet weight

1650 g of the granulate of Example 3 are mixed with 6 g magnesium stearate and pressed into oblong tablets with a weight of 331 mg and the dimensions 13 x 6 mm, radius of curvature 4.5 mm. The tablets are smooth, shiny and without cracks and contain 300 mg thioctic acid. The pressing tools are free of adhering tablet mass.
The tablets disintegrate within 2 minutes in the disintegration tester of DAB 9 (test liquid: water, 37 °C).

It is optionally possible to provide the tablets with a gastric juide-permeable, gastric juice-soluble or gastric juice-resistant film coating using conventional methods.

Example 5
Granulate with 800mg thioctic acid to 825 mg granulate

1800 g thioctic acid are mixed with 720 g of a 5 % gelatin solution in a Diosna P10 mixer granulator for 15 minutes (mixer 433 rpm, chopper 3000 rpm). The moist mass is passed through a sieve of mesh size 3.15 mm and dried in a fluidized air bed dryer (Glatt WSG 3/5) at an air inlet temperature of 30 - 35 °C to a relative moisture of 30 - 35 %. The dried granulate is passed through a sieve of mesh size 1.0 mm. The dry granulate is then mixed with 432 g of a 5 % gelatin solution in a Diosna P10 mixer granulator for 10 minutes (mixer 433 rpm, chopper 3000 rpm). The moist mass is dried in a fluidized air bed dryer (Glatt WSG 3/5) at an inlet temperature of 25 - 35 °C up to a relative moisture of 30 - 35 %. The dry granulate is passed through a sieve of mesh size 1.25 mm. The granulate can be filled into capsules or bags.

Example 6
Tablets with 800 mg thioctic acid to 835 mg tablet weight

1858 g of the granulate of Example 5 are mixed with 20 g magnesium stearate and pressed to oblong tablets, size 18 x 8 mm, weight 835 m. The tablets are smooth, shiny and without cracks and contain 800 mg thioctic acid. The pressing tools are free of adhering tablet mass, even towards the end of the pressing process. The tablets disintegrate within 3 - 5 minutes in the disintegrating tester of DAB 9 (test liquid: water, 37 °C.

Comparative Example 7
Tablets with 300 mg thioctic acid to 331 mg tablet weight

1500 g thioctic acid are mixed with 150 g hydroxypropyl cellulose. The mixture is mixed with 250 g purified water in a Diosna P10 mixer granulator for 3 minutes (mixer 215 rpm, without chopper, then for 2 minutes with the mixer at 215 rpm, chopper at 1500 rpm).

The earth-moist mass is passed through a granulating machine (Stephan KG-150P) with a ring cylinder, aperture size 2 mm. The moist granulate is dried in a fluidized air bed dryer (Glatt WSG 3/5) at an air inlet temperature of 30 - 40 °C to a relative moisture of 25 - 30 %. The dry granulate is passed through a sieve of mesh size 0.8 mm, homogeneously mixed with 6 g magnesium stearate and pressed on an eccentric or rotary press into oblong tablets with a weight of 331 mg and the dimensions 13 x 6 mm, radius of curvature 4.5 mm. The tablets already adhere to the pressing tools after only a few tablets have been pressed, fail to detach themselves completely from the pressing tools when ejected from the machine and buckle or display elongated cracks at the edge.

Example 8

Example for high dosage flupirtine tablets

1500 g flupirtine maleate are mixed with 150 g hydroxypropyl cellulose (L-HPC LH22). 1500 g purified water are added to this powder mixture and mixed in an intensive mixer, Diosna P 25 with maximum energy input for 15 minutes (mixer 350 rpm, chopper 3000 rpm). The moist mass is pre-dried on hurdles in a circulating

air drying cabinet for 30 minutes at 60 °C and passed through a sieve of mesh size 3.15 mm. The granulate is dried in a circulating air drying cabinet at 50 °C to a relative moisture of 30 - 35 % and passed through sieve of mesh size 1.0 mm. After adding 16.5 g magnesium stearate to the sieved granulate the result is mixed in a Turbula mixer, T10B for 2 minutes at 30 rpm. The mixture is pressed into biplanar tablets with a diameter of 9 mm and a weight of 143 mg. The mass can be pressed easily and without adhering to the pressing tools.
The tablets are smooth, slightly shiny and without cracks. They disintegrate in less than one minute in the disintegration tester of DAB9 (test liquid: water, 37 °C).

Example 9 for high dosage mesna tablets

Tablets with 300 mg mesna to 322 mg tablet weight

416 g corn starch are processed into corn starch paste with 2080 g water in the conventional manner.
6000 g mesna are mixed with this corn starch paste in an intensive mixer, Diosna P 25 with maximum energy input for 12 minutes (mixer 350 rpm, chopper 3000 rpm). The moist mass is pre-dried for 10 minutes at 50 °C on hurdles in a circulating air drying cabinet and then passed through a sieve of mesh size 3.15 mm. After further drying for eight hours at 50 °C in a circulating air drying cabinet the granulate is passed through a sieve of mesh size 0.8 mm. After adding 13 g magnesium stearate to the sieved granulate the result is mixed in a Turbula mixer, T10B for 5 minutes at 30 rpm. The mixture is pressed into tablets with a diameter of 9 mm, radius of curvature of 12.5 mm and a weight of 322 mg. No pressing mass adheres to the pressing tools and no coating forms, even after the machine has been running for a considerable length of time. The tablets are smooth, slightly shiny and without cracks. They disintegrate

within 5 - 7 minutes in the disintegrating tester of DAB9 (test liquid: water, 37 °C).

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A medicinal formulation in the form of tablets, pellets or granulates containing as active ingredient a compound selected from the group consisting of thioctic acid, mesna and flupirtine maleate, and having a content of said active ingredient of more than 45% by weight of the formulation; wherein said granulate or the granulate used to prepare said tablets or pellets is produced by intensive moistening of said active ingredient with more than 30 weight percent water, relative to the amount of solid substances used in the preparation of the formulation, the active ingredient being repeatedly moistened with maximum energy input in a granulator, and the formulation subsequently is dried at a temperature between 20° C and 50° C.

2. A medicinal formulation in the form of tablets, pellets or granulates containing at least one pharmaceutically-active ingredient substance, or a mixture of at least one pharmaceutically-active ingredient substance and at least one auxiliary substance, the active ingredient or ingredients being selected from the group consisting of thioctic acid, mesna and flupirtine maleate, and the formulation having a content of said an active ingredient or ingredients of more than 45% by weight of the formulation; wherein said granulate or the granulate used to prepare said tablets or pellets is produced by intensive moistening of said active ingredient or ingredients with more than 30 weight percent water, relative to the amount of solid substances used in the preparation of the formulation, the

active ingredient or ingredients being repeatedly moistened with maximum energy input in a granulator, and the formulation subsequently is dried at a temperature between 20° C and 50° C.

3. A medicinal formulation in the form of tablets, pellets or granulates as set forth in claim 1 or 2, in which the content of said active ingredient or ingredients is more than 75% by weight.

4. A medicinal formulation in the form of tablets, pellets or granulates as set forth in claim 3, in which the content of said active ingredient or ingredients is more than 85% by weight.

5. A medicinal formulation in the form of tablets, pellets or granulates containing thioctic acid (alpha-lipoic acid), wherein said granulate or the granulate used to prepare said tablets or pellets is produced by intensive moistening of thioctic acid with more than 30 weight percent water, relative to the amount of solid substances used in the preparation of the formulation, and the formulation subsequently is dried at a temperature between 20° C and 50° C.

6. A medicinal formulation in the form of tablets, pellets or granulates containing mesna, wherein said granulate or the granulate used to prepare the tablets or pellets is produced by intensive moistening of mesna with more than 30 weight percent water, relative to the amount of solid substances used in the preparation of the formulation, and

the formulation subsequently is dried at a temperature between 20° C and 50° C.

7. A medicinal formulation in the form of tablets, pellets or granulates containing the maleate of 2-amino-3-ethoxycarbonyl-amino-6-(4-fluoro)-benzylaminopyridine, wherein said granulate or the granulate used to prepare the tablets or pellets is produced by intensive moistening of the maleate of 2-amino-3-ethoxycarbonyl-amino-6-(4-fluoro)-benzylaminopyridine with more than 30 weight percent water, relative to the amount of solid substances used in the preparation of the formulation, and the formulation subsequently is dried at a temperature between 20° C and 50° C.

8. A process for the preparation of granulate or pellets, which process comprises granulating or pelleting at least one pharmaceutically-active ingredient substance, or a mixture of at least one pharmaceutically-active ingredient substance and at least one auxiliary substance, with more than 30 weight percent of water relative to the amount of the solid substances used, with maximum energy input, wherein the active ingredient or ingredients are selected from the group consisting of thioctic acid, mesna and flupirtine maleate.

9. A process for the preparation of a medicinal formulation as set forth in any one of claims 1 to 7, which process comprises repeatedly moistening the active ingredient or ingredients, in a granulator with maximum energy input, with more than 30 weight percent water, and

subsequent drying of the formulation at temperatures between 20° C and 50° C.

10. A process as set forth in claim 8, further comprising the step of converting the granulate or pellets thus obtained into tablets.

11. A process as set forth in claim 9, further comprising the step of processing the granulate into pellets or tablets.

12. A process according to any one of claims 8 to 11, in which the active ingredient is thioctic acid.

13. A process according to any one of claims 8 to 11, in which the active ingredient is mesna.

14. A process according to any one of claims 8 to 11, in which the active ingredient is flupirtine maleate.

15. A medicinal formulation in the form of granulate bodies or pellets produced by a process in which a pharmaceutically-active ingredient substance or a mixture of pharmaceutically-active ingredient substances selected from the group consisting of thioctic acid, mesna and flupirtine maleate, and auxiliary substances, are granulated at least once with more than 30 weight percent water relative to the dry weight of the solid substances used, in a granulator with maximum energy input, and the formulation subsequently is dried at a temperature between 20° C and 50° C.