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(54) **Levotiroxint tartalmazó szilárd gyógyszerészeti készítmények**

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(54) **SOLID PHARMACEUTICAL PREPARATION CONTAINING LEVOTHYROXINE**

FESTES PHARMAZEUTISCHES PRÄPARAT MIT LEVOTHYROXIN

PRÉPARATION PHARMACEUTIQUE SOLIDE CONTENANT DE LA LÉVOTHYROXINE

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Description

[0001] The invention relates to a solid pharmaceutical preparation comprising levothyroxine sodium, gelatine, citric acid and a filler. The solid pharmaceutical preparation has an improved stability.

[0002] Levothyroxine sodium is used to treat thyroid hormone deficiency, and occasionally to prevent the recurrence of thyroid cancer. In treatment of thyroid hormone deficiency very low daily doses of levothyroxine sodium are used in the range from 25 to 300μg. Due to its high potency it is very important to avoid dosage variations as this may cause serious symptoms of hypothyroidism such as as severe depression, fatigue, weight gain, constipation, cold intolerance, swelling, and difficulty concentrating, if levothyroxine sodium is underdosed, or of hypothyroidism, such as pain, heart palpitations, or cardiac arrhythmias, if levothyroxine sodium dosis is too high. Therefore, storage stability of pharmaceutical preparations containing levothyroxine sodium is a critical issue.

[0003] DE 195 41 128 teaches to stabilize thyroxine preparations by addition of sodium thiosulfate. However, the use of substances like sodium thiosulfate in pharmaceutical preparations is undesirable from the toxicological point of view.

[0004] WO 2004/096177 A1 teaches to stabilize pharmaceutical preparations containing levothyroxine sodium by providing them with a water activity below 0.4. Disadvantageously the water activity of the formulations varies with the change of relative humidity during shelf life so that additional measures have to be taken such as moisture-tight packs, which result in additional costs and waste management problems.

[0005] Patel et al. examined the effect of various pH modifying additives on the stability of levothyroxine sodium tablets (Patel H. et al: The effect of excipients on stability of levothyroxine sodium pentahydrate tablets, Int J Pharm 264 (2003) 35-43). It was found that the basic pH modifying additives sodium carbonate, sodium bicarbonate and magnesium oxide lead to improvement of the stability of levothyroxine sodium tablets whereas acid pH modifying additives tartaric acid and citric acid lead to impairment of stability.

[0006] WO 99/59551 A1 teaches that storage stability of levothyroxine sodium containing solid pharmaceutical preparations can be improved by using gelatine as a binder. As described in the introduction such stabilized formulation has been developed in order to meet the increased requirements on stability as established by the Food and Drug Administration (FDA) in 1996. According to such FDA requirements levothyroxine sodium degradation in tablets throughout their shelf life has been fixed to 10% at the most.

[0007] In 2007 the FDA has raised its requirements on stability of levothyroxine sodium containing products to further diminish the risk caused this. In fact the limit of levothyroxine sodium degradation in tablets was lowered from 10 to 5% (FDA press release from 3 Oct 2007).

[0008] There is an ongoing demand for pharmaceutical preparations having an improved stability. The pharmaceutical preparations should ensure release of active compound in accordance with the requirements, should not comprise any toxicologically unacceptable adjuvants and should be capable of storage in a stable manner over an extended time.

[0009] Surprisingly, it has been found that a solid pharmaceutical preparation which meets these requirements and has an improved storage stability can be provided if it comprises besides levothyroxine sodium, gelatine, citric acid and a filler. Therefore, when an object of the present invention is directed to a solid pharmaceutical preparation comprising levothyroxine sodium, gelatine, citric acid and a filler.

[0010] The improved stability of a solid pharmaceutical preparation is especially surprising in view of that the prior art teaching of Patel et al. (as cited above) according to which the addition of citric acid leads not only to no improvement but even to a deterioration of levothyroxine sodium in tablets.

[0011] US 6,649,186 B1 disclose effervescent granules which are prepared by hot melt extruding which may contain levothyroxine sodium. Such effervescent granules contain an acid component such as citric acid together with a basic component such as sodium carbonate or sodium bicarbonate which upon contact with water react under carbon dioxide development. The pharmaceutical preparation of the present invention is preferably not an effervescent preparation. Therefore, a further object of the present invention is directed to a solid pharmaceutical preparation, which is characterized in that it is not an effervescent preparation.

[0012] US 5,753,254 A discloses a solid fast dispersing dosage form containing thyroid hormone which may also comprise citric acid to induce the formation of saliva. Solid fast dispersing dosage forms are oral administration forms which disintegrate readily and quickly in the mouth within seconds upon contact with saliva when taken orally. The pharmaceutical preparation of the present invention is preferably not a solid fast dispersing dosage form.

[0013] Therefore, a further object of the invention is directed to a solid pharmaceutical preparation, which is characterized in that it is not a solid fast dispersing dosage form.

[0014] According to an appropriate embodiment of the invention solid pharmaceutical preparation contains 5 to 400 μg, preferably 10 to 300 μg, in particular 25 to 300 μg, of levothyroxine sodium. Preferably the solid pharmaceutical preparation contain 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 or 300 μg of levothyroxine sodium.

[0015] If levothyroxine sodium is present in micronized form, especially with a particle size from 5 μm to 25 μm, the dissolution of the solid pharmaceutical preparation improves. Therefore, a preferred object of the present invention is directed to a solid pharmaceutical preparation, which is characterized in that it contains levothyroxine sodium micronized

with a particle size from 5 μm to 25 μm.

[0016] According to an appropriate embodiment of the present invention gelatine is present in the solid pharmaceutical preparation in an amount from 0.5 to 20% by weight, preferably from 1 to 10% by weight, particularly preferably from 2 to 10% by weight, most preferably at about 5% .

[0017] According to a further appropriate embodiment of the present invention citric acid is present in the solid pharmaceutical preparation in an amount from 0.1 to 5% by weight, preferably from 0.2 to 3% by weight, particularly preferably from 0.4 to 2% by weight.

[0018] According to a preferred embodiment of the invention the pharmaceutical preparation comprises besides levothyroxine sodium liothyronine sodium a as further active ingredient. Therefore, the invention is also directed to a solid pharmaceutical preparation, which is characterized in that it comprises liothyronine sodium.

[0019] A filler is an agent increasing the bulk of the pharmaceutical preparation by providing the quantity of material which is needed to form such pharmaceutical preparation. The filler being present in the solid preparation of the present invention is preferably a sugar alcohol, a sugar, a starch, a cellulose or a mixture thereof.

[0020] Sugar alcohol is taken to mean a monosaccharide whose reactive carbonyl group has been reduced to the alcohol group, such as, for example, a hexitol or a pentitol. The solid preparation according to the invention preferably comprises hexitols, such as, for example, mannitol, sorbitol, dulcitol, xylitol or ribitol, as sugar alcohol. Particular preference is given to the presence of mannitol and/or sorbitol, most particular preference is given to mannitol.

[0021] Sugar is taken to mean a monosaccharide such as, for example, a hexitol or a pentitol and a disaccharide consisting of two monosaccharides joined by a glycosidic bond. The solid preparation according to the invention preferably comprises glucose, fructose or mannose, as a monosaccharide or lactose, saccharose or maltose, as a disaccharide. Particular preference is given to lactose.

[0022] Starch is taken to mean a polysaccharide comprising helical amylose and branched amylopectin, it is produced by green plants such as potatoes, wheat, maize, rice, and cassava. The solid preparation according to the invention preferably comprises potato starch, rice starch, maize starch or precooked starch, i.e. pregelatinized starch. Particular preference is given to maize starch and pregelatinized starch, most particular preference is given to maize starch.

[0023] Cellulose is taken to mean a polysaccharide consisting of a linear chain of several hundred to over ten thousand β(1→4) linked D-glucose. The solid preparation according to the invention preferably comprises powdered cellulose or microcrystalline cellulose, particular preferred is microcrystalline cellulose.

[0024] According to an appropriate embodiment of the present invention the solid pharmaceutical preparation is characterized in that the filler is a sugar alcohol such as sorbitol or mannitol dulcitol, xylitol or ribitol, preferably sorbitol or mannitol, particular preferably mannitol, a sugar such as glucose, fructose, mannose, lactose, saccharose or maltose, preferably lactose, saccharose or maltose, particular preferably lactose, a starch such as potato starch, rice starch, maize starch or pregelatinized starch, preferably maize starch or pregelatinized starch, particular preferably maize starch, a cellulose such as powdered cellulose or microcrystalline cellulose, preferably microcrystalline cellulose, or a mixture thereof.

[0025] According to a particularly preferred embodiment of the present invention solid pharmaceutical preparation is characterized in that the filler is mannitol and/or maize starch.

[0026] According to a appropriate embodiment of the present invention the filler is present in the solid pharmaceutical preparation in an amount from 70 to 98% by weight, preferably 80 to 98% by weight, particular preferably 85 to 95% by weight.

[0027] The stability of the solid pharmaceutical preparation can be further improved if it comprises an antioxidant selected from the group consisting of tocopherol, sodium ascorbate, propyl gallate, tertiary butylhydroquinone, butylated hydroxyanisole and butylated hydroxytoluene (BHT), preferably butylated hydroxyanisole or butylated hydroxytoluene, particular preferably butylated hydroxytoluene. Therefore, a preferred object of the invention is directed to a solid pharmaceutical preparation, which is characterized in that it further comprises an antioxidant selected from the group consisting of tocopherol, propyl gallate, tertiary butylhydroquinone, butylated hydroxyanisole and butylated hydroxytoluene, preferably hydroxyanisole or butylated hydroxytoluene, particular preferably butylated hydroxytoluene. The solid pharmaceutical preparation according to the invention comprises 0.01 to 2% by weight, preferably 0.05 to 0.5% by weight, particularly preferably 0.08 to 0.2 and most preferably 0.1 %-0.15% by weight of the antioxidant.

[0028] The solid pharmaceutical preparation can be in granule, pellet, capsule or tablet form. While capsules and tablets provide the amount of active compound intended to be taken in each case as a clearly defined individual dose, the amount of active compound required in each case can be adapted in a simple manner by means of pellets and granules.

[0029] Granules can be prepared by granulation. Pellets are solid, small, spherical medicament forms, such as, for example, granule grains or microtablets, having a very narrow particle-size range. Granules and pellets represent an independent medicament form, but can also serve as intermediate product for the production of tablets. If it is intended that predetermined amounts of active compound can be administered by means of granules or pellets, these are, in order to ensure adequate dosage accuracy, also provided as portioned granules or introduced into capsules. The solid pharmaceutical preparation according to the invention is preferably in granule, pellet, capsule or tablet form, particular

preferably in capsule or tablet form, very particular preferably in tablet form.

[0030] Therefore, a further object of the present invention is directed to a solid pharmaceutical preparation, which is characterised in that it is in granule, pellet, capsule or tablet form, particular preferably in capsule or tablet form. A very particularly preferred object of the present invention is directed to a solid pharmaceutical preparation, which is characterized in that it is a tablet.

[0031] The solid pharmaceutical preparation may contain a disintegrating agent in order to shorten the disintegration time of the tablet or granules, enabling the active compound to be released rapidly from the it. Therefore, a further object of the present invention is directed to a solid pharmaceutical preparation, which is characterised in that a disintegrating agent is present.

[0032] Appropriate disintegrating agent in the solid pharmaceutical preparation of the present invention are sodium starch glycolate, carboxymethylcellulose sodium, crosslinked carboxymethylcellulose sodium or a mixture thereof. Therefore, a further object of the present invention is directed to a solid pharmaceutical preparation which is characterized in that the disintegrating agent is sodium starch glycolate or carboxymethylcellulose sodium or a mixture thereof.

[0033] A preferred embodiment of the solid pharmaceutical preparation comprises as a disintegrating agent carboxymethylcellulose sodium, particular preferably crosslinked carboxymethylcellulose sodium. Accordingly, a preferred object of the present invention is directed to a solid pharmaceutical preparation which is characterized in that disintegrating agent is carboxymethylcellulose sodium, particular preferably crosslinked carboxymethylcellulose sodium.

[0034] Depending on the nature of the disintegrating agent, this may be present in the solid preparation according to the invention in a proportion by weight of 0.01 to 20% by weight. The solid preparation according to the invention preferably comprises 0.1 to 10% by weight, particularly preferably 1-5% by weight, of the disintegrating agent.

[0035] According to an appropriate embodiment of the invention the solid pharmaceutical preparation comprises 1 to 10% by weight of gelatine, 0.1 to 3% by weight citric acid, 50 to 80% by weight of mannitol or lactose and 10 to 30% by weight of maize starch. Therefore, a further object of the present invention is directed to a solid pharmaceutical preparation, which is characterised in that it comprises 1 to 10% by weight of gelatine, 0.1 to 3% by weight citric acid, 50 to 80% by weight of mannitol or lactose, 10 to 30% by weight maize starch.

[0036] According to an preferred embodiment of the invention the solid pharmaceutical preparation comprises 0,05 to 0,5% by weight butylated hydroxytoluene. Therefore, a further object of the present invention is directed to a solid pharmaceutical preparation, which is characterised in that it comprises 0,05 to 0,5% by weight butylated hydroxytoluene. Preferably the 0,05 to 0,5% by weight butylated hydroxytoluene are is present in the solid pharmaceutical preparation, which is characterised in that it comprises 1 to 10% by weight of gelatine, 0.1 to 3% by weight citric acid, 50 to 80% by weight of mannitol or lactose, 10 to 30% by weight maize starch.

[0037] A particular preferred object of the invention is directed to a solid pharmaceutical preparation which is characterised in that it comprises 2 to 8% by weight of gelatine, 0.5 to 2% by weight citric acid, 60 to 75% by weight of mannitol or lactose, 15 to 25% by weight of maize starch and optionally 0,08 to 0,2% by weight butylated hydroxytoluene.

[0038] If the solid pharmaceutical preparation according to the invention is a tablet, this may also comprise lubricants in order to reduce the sliding friction of the tableting material and ram in the mould during the tableting operation and to prevent sticking to the rams. Suitable lubricants are alkaline-earth metal salts of fatty acids, such as magnesium stearate or calcium stearate, fatty acids, such as stearic acid, higher fatty alcohols such al cetyl alcohol or stearyl alhohol, fats such as glyceryl dipalmitostearate, glyceryl distearate, stearin or glyceryl dibehenate, alkaline-earth metal salts of C_{16}-C_{18} alkyl substituted dicarbonic acids such as sodium stearyl fumarate, hydrated vegetable oils such as hydrated castor oil or hydrated cotton seed oil, or minerals such as silica or talc. The solid preparation according to the invention preferably comprises magnesium stearate, stearic acid or sodium stearyl fumarate as lubricant, particular preferably magnesium stearate. Lubricants are preferably present in the solid preparation according to the invention in a proportion of 0.1 to 5% by weight, preferably 0.25 to 4% by weight, particularly preferably 0,5 to 3% by weight, most preferably about 1% by weight.

[0039] The solid preparation according to the invention can be prepared by methods known to the person skilled in the art.

[0040] Granules are produced by granulation, which can basically be carried out by the moist or dry route. In the case of moist granulation, for example, a granulation liquid, which preferably comprises a binder, is added to a powder mixture comprising the active compound together with the sugar alcohol and any further suitable adjuvants, the mixture is converted into aggregates of suitable size (granules) and subsequently dried. The active compound can also be introduced into the granules by suspension in the granulation liquid. The conversion of the powder mixture into aggregates of suitable size can be carried out, for example, by so-called build-up granulation, for example in coating pans, by means of plate granulation or in fluidised-bed methods, for example by the Glatt or Wurster method, or by so-called reduction granulation, in which the powder mixture is firstly moistened and converted into a plastically mouldable mass and subsequently converted into aggregates of the desired size, for example by extrusion through a screen having meshes of suitable size. In the case of dry granulation, the powder mixture is pressed, for example, by means of compaction between two counter-rotating compaction rolls to give flakes, which are subsequently comminuted to give granules.

[0041] Pellets can be produced by granulation and subsequent rounding-off (spheronisation), for example by means of plate granulation, or alternatively by pressing powders or granules to give microtablets.

[0042] The preparation according to the invention in the form of tablets can be produced by pressing powder mixtures (direct compression) or by pressing granules. In the simplest case of direct compression, the active compound is firstly mixed with the excipients and the resultant powder mixture is pressed directly to give the solid preparation according to the invention.

[0043] According to a preferred embodiment of the invention the solid pharmaceutical preparation is prepared by a process, which is characterized in that

(a) levothyroxine sodium and optionally liothyronine sodium is/are suspended in an aqueous gelatine solution,
(b) the suspension obtained by step (a) is sprayed onto the filler in a fluidized bed granulation and dried to form granules,
(c) the granules obtained by step (b) are collected and optionally,
(d) a disintegrant and optionally a lubricant is/are mixed with the granules obtained by step (c), and
(e) the mixture obtained by step (d) is compressed to give tablets.

[0044] Accordingly, one object of the present invention is further directed to a process for the production of a solid pharmaceutical preparation, which is characterized in that

(a) levothyroxine sodium and optionally liothyronine sodium is/are suspended in an aqueous gelatine solution,
(b) the suspension obtained by step (a) is sprayed onto the filler in a fluidized bed granulation and dried to form granules,
(c) the granules obtained by step (b) are collected and optionally,
(d) a disintegrant and optionally a lubricant is/are mixed with the granules obtained by step (c), and
(e) the mixture obtained by step (d) is compressed to give tablets.

[0045] The granules obtained by performing the steps (a) to (c) can be directly used as a medicament form without performing the optional steps (d) and (e). If the granules are used they can be provided as portioned granules or introduced into capsules to ensure adequate dosage accuracy as described above.

[0046] According to a further appropriate embodiment of the invention the solid pharmaceutical preparation is prepared by a process, which is characterized in that citric acid and, if present, the antioxidant is dissolved in in the aqueous gelatine solution used in step (a) or is admixed with the granules in step (d). Therefore, a further object of the invention is directed to a process for the production of a solid pharmaceutical preparation, which is characterized in that citric acid and, if present, the antioxidant is dissolved in the aqueous gelatine solution used in step (a) or is admixed with the granules in step (d).

[0047] According to an appropriate embodiment of the invention the granules or the tablets are provided with a coating. Therefore, a further object of the invention is directed to a process for the production of a solid pharmaceutical preparation, which is characterized in that the granules or the tablets are provided with a coating.

[0048] Suitable coatings are film-forming polymers, such as, for example, those from the group of the cellulose derivatives, dextrins, starches, natural gums, such as, for example, gum arabic, xanthans, alginates, polyvinyl alcohol, polymethacrylates and derivatives thereof, such as, for example, eudragites, which may be applied to the tablet as solutions or suspensions by means of the various pharmaceutical conventional methods, such as, for example, film coating. Use is usually made here of solutions/suspensions which, besides the film-forming polymer, also comprise further adjuvants, such as hydrophilisers, plasticisers, surfactants, dyes and white pigments, such as, for example, titanium dioxide.

[0049] The examples illustrate the invention without being restricted thereto.

Example 1

[0050] Tablet (batch 015093) comprising

0.075 mg of levothyroxine sodium
68.525 mg of mannitol
20.00 mg of maize starch
5.00 mg of sodium starch glycolate
5.00 mg of gelatine
0.40 mg of citric acid
1.00 mg of magnesium stearate

[0051] The gelatin is diluted in hot water (ca. 90% of total amount of water, temperature 90°C ± 10°C) under stirring. The levothyroxine sodium is suspended in cold water (10% of total amount of water) with Ultraturrax. When the gelatin solution has cooled down to 50°C ± 5°C, the levothyroxine sodium suspension is given to it, while the final temperature of the granulation fluid is 40-45°C.

[0052] The granulation fluid containing gelatin and active compound is sprayed onto the mannitol and maize starch in the fluidised bed. The temperature of the granulation fluid is kept at around 40°C. The granules are finalized as soon a outlet air temperature has raised up to 40°C.

[0053] Citric acid, sodium starch glycolate and magnesium stearate are admixed with the granules, the resultant mixture is pressed to give tablets. Instead of admixing with the granules citric acid can also be added by dissolving it during preparation of the levothyroxine sodium containing gelatine solution.

Example 2

[0054] Tablet (batch 015099) comprising

0.30 mg of levothyroxine sodium
68.20 mg of mannitol
20.00 mg of maize starch
3.50 mg of croscarmellose sodium
5.00 mg of gelatine
2.00 mg of citric acid
1.00 mg of magnesium stearate

[0055] The tablets are produced analogous to Example 1.

Example 3

[0056] Tablet (batch 014916) comprising

0.105 mg of levothyroxine sodium
70.295 mg of mannitol
20.00 mg of maize starch
3.50 mg of croscarmellose sodium
5.00 mg of gelatine
0.10 mg of butylated hydroxytoluene
0.80 mg of citric acid
1.00 mg of magnesium stearate

[0057] The tablets are produced analogous to Example 1. The butylated hydroxytoluene is diluted in hot water (ca. 90% of total amount of water, temperature 90°C ± 10°C) under stirring. Afterwards the gelatin is given to this solution under stirring. The Levothyroxine sodium is suspended in cold water (10% of total amount of water) with Ultraturrax. As soon the BHT-gelatin solution has cooled down to 50°C ± 5°C, the levothyroxine sodium suspension is given to it, while the final temperature of the granulation fluid now is 40-45°C.

Example 4

[0058] Tablet comprising

0.300 mg of levothyroxine sodium
73.100 mg of mannitol
20.00 mg of maize starch
3.50 mg of croscarmellose sodium
2.00 mg of gelatine
0.10 mg of butylated hydroxytoluene
0.80 mg of citric acid
1.00 mg of magnesium stearate

[0059] The tablets are produced analogous to Example 3.

Example 5

[0060] Tablet comprising

0.025 mg of levothyroxine sodium
65.375 mg of mannitol
20.00 mg of maize starch
3.50 mg of croscarmellose sodium
10.00 mg of gelatine
0.10 mg of butylated hydroxytoluene
0.80 mg of citric acid
1.00 mg of magnesium stearate

[0061] The tablets are produced analogous to Example 3.

Example 6

[0062] Tablet comprising

0.105 mg of levothyroxine sodium
70.395 mg of isomalt
20.00 mg of maize starch
3.50 mg of croscarmellose sodium
5.00 mg of gelatine
0.40 mg of citric acid
1.00 mg of magnesium stearate

[0063] The tablets are produced analogous to Example 1.

Example 7

[0064] Tablet comprising

0.105 mg of levothyroxine sodium
81.645 mg of cellulose microcrystalline
3.50 mg of croscarmellose sodium
4.50 mg of gelatine
1.50 mg of citric acid
0.25 mg of magnesium stearate

[0065] The tablets are produced analogous to Example 1.

Example 8

[0066] Tablet comprising

0.105 mg of levothyroxine sodium
70.295 mg of sorbitol
20.00 mg of maize starch
3.50 mg of croscarmellose sodium
5.00 mg of gelatine
0.10 mg of butylated hydroxytoluene
0.80 mg of citric acid
1.00 mg of magnesium stearate

[0067] The tablets are produced analogous to Example 3.

Example 9

[0068] Tablet comprising

0.105 mg of levothyroxine sodium
70.295 mg of sucrose
20.00 mg of maize starch
3.50 mg of croscarmellose sodium
5.00 mg of gelatine
0.10 mg of butylated hydroxytoluene
0.80 mg of citric acid
1.00 mg of magnesium stearate

[0069] The tablets are produced analogous to Example 3.

Example 10

[0070] Tablet comprising

0.105 mg of levothyroxine sodium
70.395 mg of mannitol
20.00 mg of maize starch
3.50 mg of croscarmellose sodium
5.00 mg of gelatine
2.00 mg of citric acid
0.10 mg of sodium ascorbate
1.00 mg of magnesium stearate

[0071] The tablets are produced analogous to Example 1.

Example 11

[0072] Granules comprising

0.105 mg of levothyroxine sodium
70.295 mg of mannitol
20.00 mg of maize starch
5.00 mg of gelatine
0.10 mg of butylated hydroxytoluene
0.80 mg of citric acid

[0073] The citric acid and the gelatin are diluted in hot water (ca. 90% of total amount of water, temperature 90°C ± 10°C) under stirring. The levothyroxine sodium is suspended in cold water (10% of total amount of water) with Ultraturrax. When the gelatin solution with the citric acid has cooled down to 50°C ± 5°C, the levothyroxine sodium suspension is given to it, while the final temperature of the granulation fluid is 40-45°C.

[0074] The granulation fluid containing gelatin and active compound is sprayed onto the mannitol and maize starch in the fluidised bed. The temperature of the granulation fluid is kept at around 40°C. The granules are finalized as soon a outlet air temperature has raised up to 40°C.

Example 12

[0075]

Capsules comprising granules

Granules of example 11 filled into capsules (gelatine or HPMC)

Comparison Example 1

[0076] Tablet (batch 127494) comprising

0.105 mg of levothyroxine sodium
65.895 mg of lactose
25.00 mg of maize starch
3.50 mg of crosscarmellose sodium
5.00 mg of gelatine
0.50 mg of magnesium stearate

[0077] The tablets are produced analogous to Example 1.

Comparison Example 2

[0078] Tablet (batch 014698) comprising

0.105 mg of levothyroxine sodium
70.395 mg of mannitol
20.00 mg of maize starch
3.50 mg of crosscarmellose sodium
5.00 mg of gelatine
0.50 mg of magnesium stearate

[0079] The tablets are produced analogous to Example 1.

Comparison Example 3

[0080] Tablet (batch 014842) comprising

0.105 mg of levothyroxine sodium
70.295 mg of mannitol
20.00 mg of maize starch
3.50 mg of crosscarmellose sodium
5.00 mg of gelatine
0.10 mg of butylated hydroxytoluene
1.00 mg of magnesium stearate

[0081] The tablets are produced analogous to Example 1. Butylated hydroxytoluene was admixed as described in Example 3.

Stability testing

[0082] To assess the influence of the ingredients, especially citric acid and/or antioxidant on storage stability the pharmaceutical preparations of Examples 1 to 4 and the Comparison Examples 1 and 2 were transferred into glass bottles without closure and stored under elevated temperature and humidity (60 degree Celsius and 75% relative humidity (r.h.)). Storage times and the amounts of active compound measured in each case are shown in Table 1.

Table 1

Example	Day	Levothyroxine Sodium [µg]	Levothyroxine Sodium [%]
Preparation with citric acid			
Ex. 1	0	99.4	100
Ex. 1	14	90.2	90.7
Preparation with citric acid			
Ex. 2	0	103.5	100

(continued)

Preparation with citric acid			
Ex. 2	14	94.8	91.6
Preparation with citric acid and butylated hydroxytoluene			
Ex. 3	0	103.7	100
Ex. 3	14	96.4	93.0
Preparation without citric acid and butylated hydroxytoluene			
Comp. Ex. 1	0	105.2	100
Comp. Ex. 1	14	70	66.5
Preparation without citric acid and butylated hydroxytoluene			
Comp. Ex. 2	0	106.8	100
Comp. Ex. 2	14	93.9	87.9
Preparation without citric acid but with butylated hydroxytoluene			
Comp. Ex. 3	0	105.5	100
Comp. Ex. 3	14	93.6	88.7

[0083] As demonstrated by the data in table 1 the presence of citric acid leads to an improvement of stability which is further improved by the antioxidant. As no improvement of stability is obtained if the antioxidant is present without citric acid the antioxidant exhibits an antioxidant unexpectedly exhibits a synergistic stabilization effect in combination with citric acid.

[0084] The pharmaceutical preparations of Examples 3 and 4 and Comparison Examples were transferred into HDPE bottles, closed and stored at 40°C and 75% r.h. Storage times and the amounts of active compound measured in each case are shown in Table 2.

Table 2

Example	Weeks	Levothyroxine Sodium [μg]	Levothyroxine Sodium [%]
Preparation with citric acid and butylated hydroxytoluene			
Ex. 4	0	103.7	100
Ex. 4	13	103.7	100
Ex. 4	26	103.6	99.9
Preparation without citric acid and butylated hydroxytoluene			
Comp. Ex. 1	0	104.5	100
Comp. Ex. 1	13	102.2	97.8
Comp. Ex. 1	26	101.4	97.0
Preparation without citric acid and butylated hydroxytoluene			
Comp. Ex. 2	0	105.5	100
Comp. Ex. 2	13	102.9	97.5
Comp. Ex. 2	26	101.1	95.8
Preparation without citric acid but with butylated hydroxytoluene			
Comp. Ex. 3	0	105.5	100
Comp. Ex. 3	13	102.0	96.7
Comp. Ex. 3	26	101.8	96.5

[0085] As apparent from table 2 the presence of an antioxidant does not exhibit a significant stabilisation effect without the presence of citric acid. Further and surprisingly the combination of citric acid with the antioxidant leads to such a good stabilization effect that after half year storage at elevated temperature and humidity (40°C and 75% r.h.) the content of levothyroxine sodium in the preparation decreased only 0.1 % by weight.

Analytical test methods:

[0086] Identity, purity and assay of the solid pharmaceutical preparation comprising levothyroxine sodium are tested by high-performance liquid chromatography or ultra high performance liquid chromatography with UV detection using an reversed phase column and a gradient system after preparation and during the stability studies. The extraction medium and mobile phase used are mixtures of acetonitrile, water and phosphoric acid.

Claims

1. Solid pharmaceutical preparation comprising levothyroxine sodium, gelatine, citric acid and a filler.

2. Solid pharmaceutical preparation according to Claim 1, **characterized in that** it comprises liothyronine sodium.

3. Solid pharmaceutical preparation according to Claim 1 and/or 2, **characterized in that** the filler is a sugar alcohol such as sorbitol or mannitol dulcitol, xylitol or ribitol, preferably sorbitol or mannitol, particular preferably mannitol, a sugar such as glucose, fructose, mannose, lactose, saccharose or maltose, preferably lactose, saccharose or maltose, particular preferably lactose, a starch such as potato starch, rice starch, maize starch or pregelatinized starch, preferably maize starch or pregelatinized starch, particular preferably maize starch, a cellulose such as powdered cellulose or microcrystalline cellulose, preferably microcrystalline cellulose, or a mixture thereof.

4. Solid pharmaceutical preparation according to Claim 3, **characterised in that** the filler is mannitol and/or maize starch.

5. Solid pharmaceutical preparation according to one or more of Claims 1 to 4, **characterized in that** it further comprises an antioxidant selected from the group consisting of tocopherol, propyl gallate, tertiary butylhydroquinone, butylated hydroxyanisole and butylated hydroxytoluene, preferably hydroxyanisole or butylated hydroxytoluene, particular preferably butylated hydroxytoluene.

6. Solid pharmaceutical preparation according to one or more of Claims 1 to 5, **characterised in that** it is in granule, pellet, capsule or tablet form.

7. Solid pharmaceutical preparation according to Claim 6, **characterised in that** it is a tablet.

8. Solid pharmaceutical preparation according to one or more of Claim 1 to 7, **characterised in that** at least one disintegrating agent is present.

9. Solid pharmaceutical preparation according to Claim 8, **characterized in that** the disintegrating agent is sodium starch glycolate, or carboxymethylcellulose sodium or a mixture thereof.

10. Solid pharmaceutical preparation according to Claim 9, **characterized in that** the disintegrating agent present is carboxymethylcellulose sodium.

11. Solid pharmaceutical preparation according to one or more of Claims 1 to 10, **characterised in that** it comprises 1 to 10% by weight of gelatine, 0.1 to 3% by weight citric acid, 50 to 80% by weight of mannitol or lactose, 10 to 30% by weight maize starch.

12. Solid pharmaceutical preparation according to Claim 11, **characterised in that** it comprises 0,05 to 0,5% by weight butylated hydroxytoluene.

13. Process for the production of a solid pharmaceutical preparation according to one or more of Claims 7 to 12, **characterized in that**

(a) levothyroxine sodium and optionally liothyronine sodium is/are suspended in an aqueous gelatine solution,
(b) the suspension obtained by step (a) is sprayed onto the filler in a fluidized bed granulation and dried to form granules,
(c) the granules obtained by step (b) is collected and optionally,
(d) a disintegrant and optionally a lubricant is/are mixed with the granules obtained by step (c), and
(e) the mixture obtained by step (d) is compressed to give tablets.

14. Process for the production of a solid pharmaceutical preparation according to Claim 13, **characterized in that** citric acid and, if present, the antioxidant is dissolved in the aqueous gelatine solution used in step (a) or is admixed with the granules in step (d).

15. Process for the preparation of a solid pharmaceutical preparation according to Claims 13 and/or 14, **characterised in that** the granules or the tablets are provided with a coating.

Patentansprüche

1. Feste pharmazeutische Zubereitung enthaltend Levothyroxin-Natrium, Gelatine, Zitronensäure und ein Füllmittel.

2. Feste pharmazeutische Zubereitung nach Anspruch 1, **dadurch gekennzeichnet, dass** sie Liothyronin-Natrium enthält.

3. Feste pharmazeutische Zubereitung nach Anspruch 1 und/oder 2, **dadurch gekennzeichnet, dass** es sich bei dem Füllmittel um einen Zuckeralkohol wie Sorbitol oder Mannitol Dulcitol, Xylitol oder Ribitol, bevorzugt Sorbitol oder Mannitol, besonders bevorzugt Mannitol, einen Zucker wie Glucose, Fructose, Mannose, Lactose, Saccharose oder Maltose, bevorzugt Lactose, Saccharose oder Maltose, besonders bevorzugt Lactose, eine Stärke wie Kartoffelstärke, Reisstärke, Maisstärke oder Quellstärke, bevorzugt Maisstärke oder Quellstärke, besonders bevorzugt Maisstärke, eine Cellulose wie pulverisierte Cellulose oder mikrokristalline Cellulose, bevorzugt mikrokristalline Cellulose, oder ein Gemisch davon handelt.

4. Feste pharmazeutische Zubereitung nach Anspruch 3, **dadurch gekennzeichnet, dass** es sich bei dem Füllmittel um Mannitol und/ oder Maisstärke handelt.

5. Feste pharmazeutische Zubereitung nach einem oder mehreren der Ansprüche 1 bis 4, **dadurch gekennzeichnet, dass** sie weiterhin ein Antioxidans enthält, das aus der Gruppe bestehend aus Tocopherol, Propylgallat, tertiärem Butylhydrochinon butyliertem Hydroxyanisol und butyliertem Hydroxytoluol, bevorzugt Hydroxyanisol oder butyliertem Hydroxytoluol, besonders bevorzugt butyliertem Hydroxytoluol, ausgewählt ist.

6. Feste pharmazeutische Zubereitung nach einem oder mehreren der Ansprüche 1 bis 5, **dadurch gekennzeichnet, dass** sie in Granulat-, Pellet-, Kapsel- oder Tablettenform vorliegt.

7. Feste pharmazeutische Zubereitung nach Anspruch 6, **dadurch gekennzeichnet, dass** es sich um eine Tablette handelt.

8. Feste pharmazeutische Zubereitung nach einem oder mehreren der Anspruch 1 bis 7, **dadurch gekennzeichnet, dass** mindestens ein Sprengmittel vorhanden ist.

9. Feste pharmazeutische Zubereitung nach Anspruch 8, **dadurch gekennzeichnet, dass** es sich bei dem Sprengmittel um Natrium-Stärkeglykolat oder Carboxymethylcellulose-Natrium oder ein Gemisch davon handelt.

10. Feste pharmazeutische Zubereitung nach Anspruch 9, **dadurch gekennzeichnet, dass** es sich bei dem vorhandenen Sprengmittel um Carboxymethylcellulose-Natrium handelt.

11. Feste pharmazeutische Zubereitung nach einem oder mehreren der Ansprüche 1 bis 10, **dadurch gekennzeichnet, dass** sie 1 bis 10 Gew.-% Gelatine, 0,1 bis 3 Gew.-% Zitronensäure, 50 bis 80 Gew.-% Mannitol oder Lactose, 10 bis 30 Gew.-% Maisstärke enthält.

12. Feste pharmazeutische Zubereitung nach Anspruch 11, **dadurch gekennzeichnet, dass** sie 0,05 bis 0,5 Gew.-%

butyliertes Hydroxytoluol enthält.

13. Verfahren zur Herstellung einer festen pharmazeutischen Zubereitung nach einem oder mehreren der Ansprüche 7 bis 12, **dadurch gekennzeichnet, dass** man

(a) Levothyroxin-Natrium und gegebenenfalls Liothyronin-Natrium in einer wässrigen Gelatinelösung suspendiert,
(b) die aus Schritt (a) erhaltene Suspension in einer Fließbettgranulierung auf das Streckmittel aufsprüht und zu Granulat trocknet,
(c) das aus Schritt (b) erhaltene Granulat gewinnt und gegebenenfalls
(d) ein Sprengmittel und gegebenenfalls ein Gleitmittel mit dem aus Schritt (c) erhaltenen Granulat mischt, und
(e) das aus Schritt (d) erhaltene Gemisch zu Tabletten verpresst.

14. Verfahren zur Herstellung einer festen pharmazeutischen Zubereitung nach Anspruch 13, **dadurch gekennzeichnet, dass** Zitronensäure und, wenn vorhanden, das Antioxidans in der in Schritt (a) verwendeten wässrigen Gelatinelösung gelöst oder mit dem Granulat in Schritt (d) vermischt wird.

15. Verfahren zur Herstellung einer festen pharmazeutischen Zubereitung nach den Ansprüchen 13 und/oder 14, **dadurch gekennzeichnet, dass** das Granulat oder die Tabletten mit einem Überzug versehen werden.

Revendications

1. Préparation pharmaceutique solide comprenant de la lévothyroxine sodique, de la gélatine, de l'acide citrique et une charge.

2. Préparation pharmaceutique solide selon la revendication 1, **caractérisée en ce qu'**elle comprend de la liothyronine sodique.

3. Préparation pharmaceutique solide selon la revendication 1 et/ou 2, **caractérisée en ce que** la charge est un alcool de sucre tel que le sorbitol ou le mannitol, le dulcitol, le xylitol ou le ribitol, préférablement le sorbitol ou le mannitol, particulièrement préférablement le mannitol, un sucre tel que le glucose, le fructose, le mannose, le lactose, le saccharose ou le maltose, préférablement le lactose, le saccharose ou le maltose, particulièrement préférablement le lactose, un amidon tel que l'amidon de pomme de terre, l'amidon de riz, l'amidon de maïs ou un amidon prégélatinisé, préférablement l'amidon de maïs ou un amidon prégélatinisé, particulièrement préférablement l'amidon de maïs, une cellulose telle qu'une cellulose en poudre ou une cellulose microcristalline, préférablement une cellulose microcristalline, ou un mélange de ceux-ci.

4. Préparation pharmaceutique solide selon la revendication 3, **caractérisée en ce que** la charge est le mannitol et/ou l'amidon de maïs.

5. Préparation pharmaceutique solide selon l'une ou plusieurs parmi les revendications 1 à 4, **caractérisée en ce qu'**elle comprend en outre un antioxydant choisi dans le groupe constitué par le tocophérol, le gallate de propyle, la tertio-butylhydroquinone, l'hydroxyanisole butylé et l'hydroxytoluène butylé, préférablement l'hydroxyanisole ou l'hydroxy-toluène butylé, particulièrement préférablement l'hydroxytoluène butylé,.

6. Préparation pharmaceutique solide selon l'une ou plusieurs parmi les revendications 1 à 5, **caractérisée en ce qu'**elle se trouve sous forme de granulé, de pastille, de capsule ou de comprimé.

7. Préparation pharmaceutique solide selon la revendication 6, **caractérisée en ce qu'**il s'agit d'un comprimé.

8. Préparation pharmaceutique solide selon l'une ou plusieurs parmi les revendications 1 à 7, **caractérisée en ce qu'**au moins un agent délitant est présent.

9. Préparation pharmaceutique solide selon la revendication 8, **caractérisée en ce que** l'agent délitant est le glycolate d'amidon sodique, ou la carboxyméthylcellulose de sodium, ou un mélange de ceux-ci.

10. Préparation pharmaceutique solide selon la revendication 9, **caractérisée en ce que** l'agent délitant présent est la

carboxyméthylcellulose de sodium.

11. Préparation pharmaceutique solide selon l'une ou plusieurs parmi les revendications 1 à 10, **caractérisée en ce qu'**elle comprend de 1à 10% en poids de gélatine, de 0,1 à 3% en poids d'acide citrique, de 50 à 80% en poids de mannitol ou de lactose, de 10 à 30% en poids d'amidon de maïs.

12. Préparation pharmaceutique solide selon la revendication 11, **caractérisée en ce qu'**elle comprend de 0,05 à 0,5% en poids d'hydroxy-toluène butylé.

13. Procédé de production d'une préparation pharmaceutique solide selon l'une ou plusieurs parmi les revendications 7 à 12, **caractérisé en ce que**

(a) de la lévothyroxine sodique et éventuellement de la liothyronine sodique est/sont mise(s) en suspension dans une solution de gélatine aqueuse,
(b) la suspension obtenue dans l'étape (a) est pulvérisée sur la charge par granulation en lit fluidisé pour et séchée afin de former des granulés,
(c) les granulés obtenus dans l'étape (b) sont récupérés et éventuellement,
(d) un agent délitant et éventuellement un lubrifiant est/sont mélangé(s) avec les granulés obtenus dans l'étape (c), et
(e) le mélange obtenu dans l'étape (d) est mis sous forme de comprimés.

14. Procédé de production d'une préparation pharmaceutique solide selon la revendication 13, **caractérisé en ce que** l'acide citrique et, s'il est présent, l'antioxydant, est/sont dissous dans la solution de gélatine aqueuse utilisée dans l'étape (a) ou est/sont mélangé(s) avec les granulés dans l'étape (d).

15. Procédé de préparation d'une préparation pharmaceutique solide selon les revendications 13 et/ou 14, **caractérisé en ce que** les granulés ou les comprimés sont pourvus d'un revêtement.

REFERENCES CITED IN THE DESCRIPTION

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- **PATEL H. et al.** The effect of excipients on stability of levothyroxine sodium pentahydrate tablets. *Int J Pharm,* 2003, vol. 264, 35-43 **[0005]**

Szabadalmi igénypontok

1. Szilárd gyógyszerészeti készítmény, amely tartalmaz levotiroxin-nátriumot, zselatint, citromsavat és töltőanyagot.

2. Az 1. igénypont szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy tartalmaz liotironin-nátriumot.

3. Az 1. és/vagy 2. igénypontok szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy a töltőanyag egy cukoralkohol, mint szorbit vagy mannit, dulcit, xilit vagy ribit, előnyösen szorbit vagy mannit, különösen előnyösen mannit, egy cukor, mint glükóz, fruktóz, mannóz, laktóz, szacharóz vagy maltóz, előnyösen laktóz, szacharóz vagy maltóz, különösen előnyösen laktóz, egy keményítő, mint burgonyakeményítő, rizskeményítő, kukoricakeményítő vagy előzselatinozott keményítő, előnyösen kukoricakeményítő vagy előzselatinozott keményítő, különösе előnyösen kukoricakeményítő, egy cellulóz, mint porított cellulóz vagy mikrokristályos cellulóz, előnyösen mikrokristályos cellulóz, vagy ezek keveréke.

4. A 3. igénypont szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy a töltőanyag mannit és/vagy kukoricakeményítő.

5. Az 1-4. igénypontok közül egy vagy több szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy tartalmaz továbbá egy oxidánst a következőkből álló csoportból választva: tokoferol, propil-gallát, tercier butilhidrokinon, butilezett hidroxianizol és butilezett hidroxitoluol, előnyösen hidroxianizol vagy butilezett hidroxitoluol, különösen előnyösen butilezett hidroxitoluol.

6. Az 1-5. igénypontok közül egy vagy több szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy granulátum, pellet, kapszula vagy tabletta formájú.

7. A 6. igénypont szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy tabletta.

8. Az 1-7. igénypontok közül egy vagy több szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy legalább egy dezintegráló szer van jelen.

9. A 8. igénypont szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy a dezintegráló szer nátrium-keményítő-glikolát vagy karboximetil-cellulóz-nátrium vagy ezek keveréke.

10. A 9. igénypont szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy a jelenlévő dezintegráló szer a karboximetil-cellulóz-nátrium.

11. Az 1-10. igénypontok közül egy vagy több szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy tartalmaz 1-10 tömeg% zselatint, 0,1-3 tömeg% citromsavat, 50-80 tömeg% mannitot vagy laktózt, 10-30 tömeg% kukoricakeményítőt.

12. A 11. igénypont szerinti szilárd gyógyszerészeti készítmény, azzal jellemezve, hogy tartalmaz 0,05 – 0,5 tömeg% butilezett hidroxitoluolt.

13. Eljárás 7-12. igénypontok közül egy vagy több szerinti szilárd gyógyszerészeti készítmény előállítására, azzal jellemezve, hogy

(a) levotiroxin-nátriumot és adott esetben liotironin-nátriumot szuszpendálunk egy vizes zselatin oldatba,

(b) az (a) lépésben kapott szuszpenziót a töltőanyagra permetezzük egy fluid ágyas granulálás során, és szárítjuk szemcsék kialakítására.

(c) a (b) lépésben kapott szemcséket összegyűjtjük, és adott esetben

(d) dezintegráló szert és adott esetben kenőanyagot keverünk a (c) lépésben kapott szemcsékhez és

(e) a (d) lépésben kapott keveréket tablettákká préseljük.

14. A 13. igénypont szerinti eljárás szilárd gyógyszerészeti készítmény előállítására, azzal jellemezve, hogy citromsavat, és ha jelen van, antioxidánst oldunk az (a) lépés szerinti vizes zselatin oldatban vagy a (d) lépésben kapott szemcsékkel keverünk össze.

15. A 13. és/vagy 14. igénypont szerinti eljárás szilárd gyógyszerészeti készítmény előállítására, azzal jellemezve, hogy a szemcséket vagy tablettákat fedőréteggel látjuk el.