

ORAL THYROID THERAPEUTIC AGENT

The present invention relates to an oral thyroid therapeutic agent containing levothyroxine and/or liothyronine as the active ingredient, with improved drug stability.

Levothyroxine ($C_{15}H_{11}I_4NO_4$, $M_r = 776.9$ g/mol) corresponds to the endogenous thyroid hormone known as thyroxine or T4 and is an international non-proprietary name (INN). Levothyroxine is the tetraiodinated derivative of the amino acid tyrosine. Medicinal products mainly use the sodium salt of levothyroxine, which is referred to as L-thyroxine-Na or levothyroxine sodium. Levothyroxine is also a precursor of triiodothyronine or T3, which is also referred to as liothyronine.

The active ingredient thyroxine and also its enantiomers in pure form do not have sufficient stability to store oral pharmaceuticals containing these for a long period of time. Therefore, it is necessary to provide galenic preparations that ensure sufficient stability of the active ingredient and the entire preparation, in as many climate zones as possible.

One approach to this end is to use special packaging that binds or deters atmospheric oxygen from the preparation containing the active ingredient levothyroxine. Such devices are described, for example, in US 2009/0297566 A1 or EP 1 772 395 A1.

A number of levothyroxine preparations with improved stability are already known in the state of the art. To accomplish this, stabilizers are added to the preparations. In WO 2003/041699 A1 and US 8,779,000 B1 the addition of antioxidants is proposed.

However, there are also compositions that do not contain certain, otherwise usual ingredients because they negatively affect the stability of levothyroxine. For example, these compositions are described, in US 8,779,000 B1 or DE 198 30 246 A1. In DE 198 30 246 A1 the exclusion of antioxidants is explicitly proposed.

Also known are preparations in which the active ingredient levothyroxine is encapsulated or embedded by means of certain excipients. Such preparations are described in WO 1998/18610 A1.

Also known is the addition of iodine-containing compounds, such as potassium iodide, to stabilize the composition.

However, the issue regarding stability of oral thyroid therapeutics has not yet been satisfactorily resolved. Thus, there is a continuing need for stable oral preparations of thyroid therapeutics with the active ingredient levothyroxine and/or liothyronine.

The problem of the present invention is therefore to improve the stability of oral dosage forms containing levothyroxine and/or liothyronine. In particular, it is the problem of the present invention to provide an oral dosage form which meets the stability requirements for finished medicinal products in climate zone II (25 °C, 60% relative humidity) and climate zone IVB (30 °C, 75% relative humidity).

The problem is solved by providing an oral thyroid therapeutic with the features of the main claim. Advantageous embodiments of the oral thyroid therapeutics according to the invention are identified in the dependent subclaims.

The object of the present invention is an oral thyroid therapeutic agent containing at least one active ingredient in the form of a thyroid hormone or its pharmaceutically acceptable salts as active ingredient in combination with at least one antioxidant and at least one adsorbent, wherein the ratio of active ingredient : antioxidant : adsorbent, in wt.-%, is 1 : 1 : 5 to 1 : 50 : 100.

To calculate the ratio, it can be assumed that the oral thyroid therapeutic agent according to the invention, beside the active ingredient, the antioxidant and the adsorbent, together with further pharmaceutically acceptable carriers and excipients comprises a total of 100 wt.-%.

A further advantageous embodiment of the oral thyroid therapeutic according to the invention is characterized in that the active ingredient is in the form of the thyroid hormone levothyroxine or its pharmaceutically acceptable salts or

liothyronine or its pharmaceutically acceptable salts or that mixtures of said active ingredients are included.

Furthermore preferred is an oral thyroid therapeutic agent in which a further active ingredient is contained, wherein the further active ingredient is preferably at least one iodine salt selected from iodides or iodates of the alkali metals, in particular potassium iodide or potassium iodate, and mixtures of said iodine salts.

According to the invention an oral thyroid therapeutic agent is preferred, wherein pharmaceutically acceptable excipients, carriers and/or diluents are furthermore included.

Also preferred according to the invention is an oral thyroid therapeutic agent, wherein the antioxidant is selected from sulphur-containing organic antioxidants.

Here it is particularly preferred that the sulphur-containing, organic antioxidants are selected from cysteine, cystine, glutathione, dimercaptopropane sulphonic acid and their salts and derivatives and from mixtures of the aforementioned agents.

It is especially preferred that the sulphur-containing, organic antioxidant is cysteine.

Also preferred according to the invention is an oral thyroid therapeutic agent, wherein the adsorbent is selected from inorganic adsorbents. Inorganic adsorbents which are basic or oxidic are preferred among them.

Here it is particularly preferred that the inorganic adsorbents are selected from silica gels, zeolites, alkaline earth metal oxides, alkali carbonates, alkali bicarbonates, alkaline earth metal carbonates, alkaline earth bicarbonates, alkaline earth silicates and mixtures of the aforementioned adsorbents.

It is in particular preferred that the alkaline earth metal oxide is magnesium oxide and/or that the alkaline earth silicate is magnesium silicate hydrate (talc) and/or the alkali carbonate is sodium carbonate.

Furthermore preferred according to the invention is an oral thyroid therapeutic agent, wherein the ratio in wt.-% of active ingredient : antioxidant : adsor-

bent is 1 : 5 : 5 to 1 : 10 : 40.

Furthermore preferred according to the invention is an oral thyroid therapeutic agent with an active ingredient content of 0.01 to 0.5 wt.-%.

Also preferred is an oral thyroid therapeutic agent, wherein the active ingredient content of a single dosage is 25 µg to 300 µg. Especially preferred is an active ingredient content of 25 µg to 150 µg.

According to the invention, it is furthermore preferred that the content of cysteine is 0.1 – 5 wt.-%.

According to the invention, it is preferred that the content of MgO is 0.5 – 10 wt.-%. Magnesium oxide can adsorb volatile compounds by forming Van der Waals bonds.

According to the invention it is preferred that the preparation additionally contains pregelatinized starch. Here especially preferred are portions of 30 – 60 wt.-%.

Furthermore according to the invention it is preferred that microcrystalline cellulose is contained. Here especially preferred are portions of 10 – 30 wt.-%.

Additionally it is preferred according to the invention that corn starch is contained. Here especially preferred are portions of 10 – 50 wt.-%.

Preferred oral thyroid therapeutic agents are characterized in that the active ingredient content is 0.01 – 1 wt.-%. Here it is particularly preferred that the active ingredient content is 0.1 - 0.5 wt.-%.

This means that an oral thyroid therapeutic agent according to the invention has the following composition in wt.-%:

Levothyroxine sodium	0.01 – 1%
Further active ingredients	0 – 10%
Antioxidants	0.01 – 50%
Adsorbents	0.05 – 99%
Tableting excipients	ad 100%

Particular preferred are oral thyroid therapeutic agents according to the invention which have the following composition in wt.-%:

Levothyroxine sodium	0.1 – 0.5%
Further active ingredients	0 – 10%
Antioxidants	0.5 – 5%
Adsorbents	0.5 – 40%
Tableting excipients	ad 100%

Further preferred are oral thyroid therapeutic agents according to the invention which have the following composition in wt.-%:

Liothyronine sodium	0.01 – 1%
Further active ingredients	0 – 10%
Antioxidants	0.01 – 50%
Adsorbents	0.05 – 99%
Tableting excipients	ad 100%

Also preferred are oral thyroid therapeutic agents according to the invention which have the following composition in wt.-%:

Levothyroxine sodium	0.1 – 0.5%
Liothyronine sodium	0.01 – 0.5%
Antioxidants	0.5 – 5%
Adsorbents	0.5 – 40%
Tableting excipients	ad 100%

Also preferred according to the invention are oral thyroid therapeutic agents which have the following composition in wt.-%:

Levothyroxine sodium	0.1 – 0.5%
Iodine salts	0.01 – 5%
Antioxidants	0.5 – 5%
Adsorbents	0.5 – 40%
Tableting excipients	ad 100%

Surprisingly, it was found that the antioxidant and the adsorbent must be present in a high stoichiometric excess in relation to the active ingredient in the preparation according to the invention in order to achieve the desired stability of the active ingredient. It was found that advantageously a 10-fold to 50-fold stoichiometric excess of antioxidants must be selected, in relation to the active ingredient. The same applies to the adsorbent. Again, a 10-fold to 50-fold stoichiometric excess in relation to the active ingredient, is advantageous.

Furthermore it is also preferred according to the invention that the oral thyroid therapeutic agent is in the form of a base preparation with tablets which can be divided once or several times. Particularly preferred are divisible tablets which have a breaking groove, multiple breaking grooves, arranged parallel to one another, or a cross-breaking groove. This makes it possible to achieve individual dosages in patients without having to provide or prepare a separate drug for each dosage.

Brief description of the drawings

FIG. 1 shows the test results of Example 4, namely the results of the stability testing of the oral thyroid therapeutic agents according to the invention.

FIG. 2 shows the dissolution profile of the preparation according to the invention according to Example 3, namely the results of the determination of the release rate are described.

The present invention thus relates to a concept and method for the preparation of a thyroid therapeutic agent in different dosage strengths from a base granulate which is prepared from the base preparation to obtain a linear pharmacokinetics for the thyroid hormone contained after its oral administration, depending on the given dose.

The drugs of the invention are prepared in a known manner with the usual solid or liquid excipients, carriers and/or diluents and the excipients generally used in accordance with the desired mode of administration with a suitable dosage. The preferred preparations consist of a dosage form which is suitable for oral administration. Such dosage forms are, for example, solutions, suspensions, tablets, film-coated tablets, capsules or special sustained-release dosage forms.

Corresponding sustained-release forms can be prepared by mixing the active ingredient, together with the antioxidant and the adsorbent in the combination according to the invention, with known excipients or agents for achieving a depot effect. The tablets can also consist of several layers.

Accordingly, microtablets can also be produced, which can then be filled into capsules. But the powder/granules of the base recipe can also be filled directly into capsules. With conventional capsule filling machines it is therefore possible to prepare differently dosed preparations without major changeover times, since the identical base formulation is always used. Producing differently dosed forms only requires an adjustment of the fill quantity.

Accordingly sugar-coated tablets can be produced by coating cores, that were produced analogously to the tablets, with agents generally used in sugar-coatings, for example polyvinylpyrrolidone or shellac, gum arabic, talc, titanium dioxide or sugar. In this case, the coated tablet shell may also consist of several layers, wherein excipients known to the person skilled in the art may be used.

The preparation of the oral pharmaceutical preparations according to the invention is generally known and described in manuals known to the person skilled in the art (e.g. Hager, Hagers Handbuch der Pharmazeutischen Praxis-

is, 5th edition, Springer Verlag, 1999, List et al., Arzneiformenlehre, 2nd edition, Wissenschaftliche Verlagsgesellschaft 1985, Bauer et al., Pharmazeutische Technologie, 9th edition, Wissenschaftliche Verlagsgesellschaft mbH, 2012).

The oral thyroid therapeutic agent according to the invention shows a high stability in all climate zones. The storage stability compared to conventional preparations is significantly improved. This makes it possible to provide a preparation for all climate zones. Moreover, it is possible to provide various dosage forms by means of a single base preparation. This simplifies preparation and storage of the preparations and reduces costs.

The following examples further illustrate the invention in more detail without limiting the scope of the invention.

Example 1

Table I provides a formulation for a composition of an oral thyroid therapeutic agent according to the invention. Herein the ratio in wt.-% of active ingredient : antioxidant : adsorbent is 1 : 7 : 32.

Table I

Component	wt.-%
L-thyroxine Na x 5 H ₂ O	0.1
Microcrystalline cellulose	19.2
Pregelatinized starch	44.8
Corn starch	30.0
L-cysteine x HCl x H ₂ O	0.7
Magnesium oxide	3.2
Sodium carbonate	2.0
	100.0

Example 2

Table II provides a formulation for a composition of an oral thyroid therapeutic agent according to the invention. Herein the ratio in wt.-% of active ingredient : antioxidant : adsorbent is 1 : 5 : 47.

Table II

Component	wt.-%
L-thyroxine Na x 5 H ₂ O	0.1
Microcrystalline cellulose	58.5
Corn starch	34.2
L-cysteine x HCl x H ₂ O	0.5
Magnesium oxide	4.7
Talc	2.0
	100.0

Example 3

Table III provides a formulation for a composition of an oral thyroid therapeutic according to the invention. Herein the ratio in wt.-% of active ingredient : antioxidant : adsorbent is 1 : 5 : 32.

Table III

Component	wt.-%
L-thyroxine Na x 5 H ₂ O	0.1
Microcrystalline cellulose	19.2
Pregelatinized starch	45.0
Corn starch	30.0
L-cysteine x HCl x H ₂ O	0.5
Magnesium oxide	3.2
Talc	2.0
	100.0

Example 4**Stability of the oral thyroid therapeutic agents according to the invention**

Using the formulation according to Example 3, tablets were prepared with an active ingredient amount of 100 µg levothyroxine-Na. In addition, the same tablets were prepared without the antioxidant (cysteine) and without the adsorbent (magnesium dioxide). These two preparations were then subjected to a stress test together with a commercial product (Letrox® 100). In this case, the preparations were stored for 12 days at a temperature of 70 °C and a

relative humidity of 100%. The amount of active ingredient was determined before storage and after 3, 6, 9 and 12 days of storage. The test results are shown in Figure 1. It turns out that, after 12 days, the formulation according to Example 3 (with antioxidant and adsorbent) only showed a very small reduction in the active ingredient amount.

Example 5

Preparation of differently dosed levothyroxine sodium tablets

Using the formulation of Example 1, it is possible to produce differently dosed tablets solely by varying the tablet mass. The percentage composition and thus also the ratio between active ingredient (levothyroxine), antioxidant and adsorbent and excipients remains unchanged.

Using the composition of the individual components provided in Table I of Example 1 as a starting point, a tableting mixture is prepared which contains 100 µg of active ingredient in a 104 mg mixture. According to the tablet mass selected during pressing the dosage of the active ingredient can then be adjusted. This is demonstrated in the following overview.

Dosage 25 µg	tablet mass: 26.0 mg
Dosage 50 µg	tablet mass: 52.0 mg
Dosage 75 µg	tablet mass: 78.0 mg
Dosage 100 µg	tablet mass: 104.0 mg
Dosage 125 µg	tablet mass: 130.0 mg
Dosage 150 µg	tablet mass: 156.0 mg
Dosage 175 µg	tablet mass 182 mg
Dosage 200 µg	tablet mass 208 mg
Dosage 300 µg	tablet mass 312 mg

However, to use break grooves, it may be necessary to increase the tablet size to provide better breakability. In this case, the tablet mass is doubled for the 100 µg dosage and is then 208 mg. It should be noted that the ratio of active ingredient to antioxidant and adsorbent is not changed. For this purpose, it is necessary to increase the amounts of the other tableting excipients accordingly, without changing the ratio according to the invention of active

ingredient, antioxidant and adsorbent. The tablet mass to be chosen when pressing the tablets is shown in the following overview.

Dosage 25 µg	tablet mass: 52.0 mg
Dosage 50 µg	tablet mass: 104.0 mg
Dosage 75 µg	tablet mass: 156.0 mg
Dosage 100 µg	tablet mass: 208.0 mg
Dosage 125 µg	tablet mass: 260.0 mg
Dosage 150 µg	tablet mass: 312.0 mg

Example 6

Determination of the release rate

FIG. 2 shows the dissolution profile of the preparation according to the invention according to Example 3. The tablets with a mass of 104 mg have an active ingredient content of 100 µg. The tests were carried out in a paddle apparatus at 100 min⁻¹. The volume of the release medium is 500 ml; the release medium is phosphate buffer with a pH of 7.4.

After 15 minutes, 80% of the active ingredient is already released, after 60 minutes more than 90%.

This shows that the substances used to stabilize the active ingredient, namely antioxidants and adsorbents, do not adversely affect the release and thus also the bioavailability.

Patent claims

1. An oral thyroid therapeutic agent, containing at least one active ingredient in the form of a thyroid hormone or its pharmaceutically acceptable salts in combination with at least one antioxidant and at least one adsorbent, wherein the ratio of active ingredient : antioxidant : adsorbent in wt.-% is 1 : 1: 5 to 1 : 50 : 100.
2. An oral thyroid therapeutic agent, according to claim 1, characterized in that the active ingredient is in the form of the thyroid hormone levothyroxine or its pharmaceutically acceptable salts or liothyronine or its pharmaceutically acceptable salts or that mixtures of said active ingredients are included.
3. An oral thyroid therapeutic agent, according to claim 1 or 2, characterized in that a further active ingredient is contained, wherein the further active ingredient is preferably at least one iodine salt selected from iodides or iodates of the alkali metals, in particular potassium iodide or potassium iodate, and mixtures of said iodine salts.
4. An oral thyroid therapeutic agent, according to least one of the preceding claims, characterized in that furthermore pharmaceutically acceptable excipients, carriers and/or diluents are included.
5. An oral thyroid therapeutic agent, according to at least one of the preceding claims, characterized in that the antioxidant is selected from sulphur-containing, organic antioxidants.
6. An oral thyroid therapeutic agent, according to claim 5, characterized in that the sulphur-containing, organic antioxidants are selected from cysteine, cystine, glutathione, dimercaptopropane sulphonic acid and their salts and derivatives and from mixtures of the aforementioned agents.
7. An oral thyroid therapeutic agent, according to claim 6, characterized in that the sulphur-containing organic antioxidant is cysteine.

8. An oral thyroid therapeutic agent, according to at least one of the preceding claims, characterized in that the adsorbent is selected from inorganic adsorbents.
9. An oral thyroid therapeutic agent, according to claim 8, characterized in that the inorganic adsorbent is selected from silica gels, zeolites, alkaline earth metal oxides, alkali metal carbonates, alkaline bicarbonates, alkaline earth metal carbonates, alkaline earth bicarbonates and mixtures of the aforementioned adsorbents.
10. An oral thyroid therapeutic agent, according to claim 9, characterized in that the alkaline earth metal oxide is magnesium oxide and/or the alkaline earth metal silicate is talc and/or the alkali carbonate is sodium carbonate.
11. An oral thyroid therapeutic agent, according to at least one of the preceding claims, characterized in that the ratio of active ingredient : antioxidant : adsorbent in wt.-% is 1 : 5 : 5 to 1 : 10 : 40.
12. An oral thyroid therapeutic agent, according to at least one of the preceding claims, characterized in that the active ingredient content is 0.01 to 0.5 wt.-%.
13. An oral thyroid therapeutic agent, according to at least one of the preceding claims, characterized in that the active ingredient content of a single dosage is 25 µg to 150 µg.
14. An oral thyroid therapeutic agent, according to at least one of the preceding claims, in the form of tablet which can be divided once or several times.
15. An oral thyroid therapeutic agent, according to claim 14, characterized in that the divisible tablet has a breaking groove, multiple breaking grooves, arranged parallel to one another, or a cross-breaking groove.