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(54) Benævnelse: **Fremgangsmåde til fremstilling af en levothyroxinopløsning**

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DESCRIPTION

FIELD OF THE INVENTION

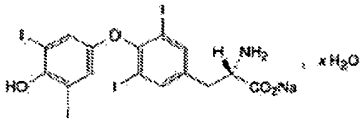
[0001] The invention relates to a method for the preparation of an oral levothyroxine composition.

BACKGROUND OF THE INVENTION

[0002] Levothyroxine, also known as L-thyroxine, synthetic T4, or 3,5,3',5'-tetraiodo-L-thyronine, CAS number 51-48-9, is a synthetic form of thyroxine, used as a hormone substitute for patients with thyroid conditions, such as hypothyroidism, as well as conditions in which the thyroid gland becomes enlarged, causing swelling of the neck.

[0003] Thyroid hormones regulate multiple metabolic processes and play an essential role in normal growth and development, and normal maturation of the central nervous system and bone. Levothyroxine sodium was initially manufactured as synthetic T4 in 1958 and it was first introduced into the market as early as before 1962 without an approved NDA, apparently in the belief that it was not a new drug.

[0004] Levothyroxine sodium is very slightly soluble in water and slightly soluble in ethanol (96 per cent). Levothyroxine sodium is described in the European Pharmacopoeia. The chemical designation of Levothyroxine sodium is Sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoate. Its molecular formula is C15H10I4NnaO4, xH2O and its molecular weight is 799 (anhydrous substance). The structural formula is:



[0005] Orally administered levothyroxine sodium is used as replacement therapy in conditions characterized by diminished or absent thyroid function such as cretinism, myxedema, non-toxic goiter, or hypothyroidism (Food and Drug Administration 1997; Wertheimer and Santella 2005).

[0006] Levothyroxine Sodium Oral Solution is indicated for:

- hypothyroidism (congenital or acquired)
- diffuse non toxic goitre or Hashimoto's thyroiditis
- thyroid carcinoma

[0007] The treatment of any thyroid disorder should be determined on an individual basis, taking account of clinical response, biochemical tests and regular monitoring. A pre-therapy ECG is valuable as changes induced by hypothyroidism may be confused with evidence of ischaemia. If too rapid an increase of metabolism is produced (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce the dose or withhold for 1-2 days and start again at a lower dose.

[0008] Oral solutions of levothyroxine are particularly suitable for use in children and in the elderly who may have difficulty to swallow tablets. Unfortunately, solutions of levothyroxine are less stable compared to tablets during storage. Also, levothyroxine solutions may comprise relatively high amounts of liothyronine, which is believed to be the source of side-effects in certain patients. Aqueous levothyroxine solutions are prone to decomposition compared to the solid forms. The big advandage of the solution is the uniformity of dosage units in comparison to solid dosage forms (tablets). The tablets, usually due to the very low levothyroxine content (0.04% up to 0.5% w/w), have problems of content uniformity during the production process and many times the actual content that the patient receives with tablet therapy, is not 100% but could range from 85% up to 120% and this creates serious problems on patient treatment. In contrast, it is much easier to obtain a homogeneous solution.

OBJECT AND SUMMARY OF THE INVENTION

[0009] It is an object of the invention to provide a more stable levothyroxine solution. It is another object of the solution to provide a levothyroxine solution that comprises less liothyronine. It is yet another object of the invention to enable a faster method for the preparation of oral levothyroxine solutions.

[0010] The invention provides a method for the preparation of an oral levothyroxine composition, comprising the steps of:

1. a) providing a salt of levothyroxine, preferably the sodium salt of levothyroxine
2. b) mixing levothyroxine with an aqueous solvent, the aqueous solvent being a mixture of water and a water miscible organic solvent, the water miscible organic solvent comprising glycerol,
3. c) adjusting the pH to a pH of at least 8 to yield a basic aqueous solvent, and
4. d) dissolving the levothyroxine in the basic aqueous solvent to yield a levothyroxine solution, and
5. e) lowering the pH of the clear levothyroxine solution to between 5-6, preferably to about 5.5.

[0011] Surprisingly, this method results in a levythyroxine solution which is more stable during storage. The obtained solution also comprises less liothyronine. Also, the preparation is relatively fast; in particular the dissolving of levothyroxine in the basic aqueous solvent is relatively fast compared to dissolving in neutral or acidic water (pH<7) or aqueous solvents of otherwise the same composition.

[0012] The provided levothyroxine salt and other ingredients are all of pharmaceutical quality. The pH is determined and monitored, preferably using a calibrated electronic pH meter based on electrode potential. In order to determine the pH during adjusting the pH, the end pH 5-6 is suitable for storage as well as for administering the levothyroxine solution to a patient. As levothyroxine may show degradation under the influence of UV and blue light, the process is preferably performed in the dark or in dark glass comprising a UV-filter.

[0013] Best results are obtained when in step c) the pH is adjusted to from 9 to 11, preferably to about 10.

[0014] It is preferred if the adjusting of the pH was done by adding a base. It is preferred if the base is added as an aqueous solution, for instance with a concentration in the order of 0.1-2 mol/l. Suitable bases comprise Potassium Bicarbonate, Potassium Citrate, Potassium Citrate, Potassium Hydroxide, Sodium Carbonate, Calcium Hydroxide, Ammonia Solution, Sodium Hydroxide, Sodium Borate, Monoethanolamine, Sodium Citrate Dihydrate, Diethanolamine, Triethanolamine and Sodium Bicarbonate. Preferably, the added base is a sodium hydroxide solution. Adding sodium hydroxide is pharmaceutically acceptable base which yielded a stable solution.

[0015] Advantageously, the adjusting of the pH in step e) was done using a carboxylic acid. Carboxylic acids, preferably water-soluble carboxylic acids, showed a good stability. Suitable carboxylic acids comprise Laurie Acid, Tartaric Acid, Acetic Acid, Glacial, Maleic Acid, and Sorbic Acid. In a preferred embodiment, the carboxylic acid is citric acid, which was well tolerated, compatible with levothyroxine and gave good results.

[0016] The aqueous solvent was a mixture of water and a water-miscible organic solvent or solubilizer. Water miscible organic solvents improved the speed of dissolving and gave a stable solution. The water-miscible organic solvent comprises glycerol.

[0017] It is preferred if, in step b), levothyroxine is mixed with the aqueous solvent while heating the mixture to 30 - 70 °C, preferably from 40-50 °C, more preferably from 40-45 °C. Raising the temperature significantly speeded up the dissolving of levothyroxine. Too high a temperature may however give rise to an increase in degradation products and lower stability of the final product.

[0018] Advantageously, also a preservative is added to the aqueous solvent. This yield an increased stability during storage. Suitable preservatives comprise Bronopol, Imidurea, Potassium Sorbate, Phenoxyethanol, Phenylmercuric Acetate, Butylparaben, Benzyl Alcohol, Phenylmercuric Borate, Chlorocresol, Benzethonium Chloride, Phenylethyl Alcohol, Benzalkonium Chloride, Methylparaben, Hexetidine, Chlorobutanol, Ethylparaben, Propylparaben, Sodium Benzoate, Potassium Benzoate, Sorbic Acid, Cresol, Propylparaben Sodium, Cetylpyridinium Chloride, Phenylmercuric Nitrate, Chloroxylenol, Propionic Acid, Phenol, Thimerosal, Sulfur Dioxide, Boric Acid, Edetic Acid, Sodium Propionate, Calcium Chloride, Sodium Acetate, Sodium Sulfite, Benzoic Acid, Monothioglycerol, Cetrimide, Calcium Acetate, Butylene Glycol, Sodium Metabisulfite, Alcohol, Propyl Gallate, Potassium Metabisulfite, Sodium Lactate, Chlorhexidine, Calcium Lactate, Pentetic Acid, Glycerin, Propylene Glycol Alginate,

Sodium Borate, Magnesium Trisilicate, Isopropyl Alcohol, Dimethyl Ether, Propylene Glycol, Butylated Hydroxyanisole, Pyrrolidone, Lactic Acid, Sodium Lauryl Sulfate and Dimethyl Sulfoxide. Preferably, the preservative is sodium methylparaben, which showed a good compatibility with levothyroxine.

[0019] The invention further provides a liquid oral Levothyroxine composition obtainable using the method according to invention.

[0020] Preferably, the composition comprises a sodium levothyroxine concentration of approximately 25 µg in 5 ml, approximately 50 µg in 5 ml or approximately 100 µg in 5 ml.

[0021] In a preferred embodiment the composition comprises sodium levothyroxine, glycerol, water and a preservative.

[0022] In a preferred embodiment, the Oral Levothyroxine composition is packed in a unit dose system selected from the group consisting of ampoules, sachets, vial,s blister packs, tubes, of stick packs, wherein the unit dose is arranged to deliver separate doses of levothyroxine from 25 up to 300mcg per single dose.

DESCRIPTION OF PREFERRED EMBODIMENTS

[0023] The invention will now be elucidated by the following non-limiting embodiments.

PROCESS DESCRIPTION

[0024] As L-Thyroxine may degrade under the influence of light, the process was performed shielded from direct sunlight. The process was otherwise performed using regular manufacturing equipment. The basic steps are as follows:

After weighing the excipients and the active ingredient, a premix was prepared by dispersing the sodium salt of L-thyroxine (Levothyroxine sodium) in glycerol, in the ratio of 1 part of levothyroxine and 100 parts of glycerol by weight. Optionally, already part of the water may be added in this premix step, keeping the amount of water below the amount of glycerol. The dispersion is agitated and heated for 15-30 minutes while maintaining the temperature between 40 and 50 °C, during which part of the L-thyroxine Na dissolves. In a separate vessel, the remaining amount of water was stirred while adding 1N NaOH solution in water until a pH of approximately 10 was obtained. This basic solution was added to the partly dissolved L-Thyroxine Na dispersion. The final mixture was stirred at room temperature (20-25°C) until a clear homogeneous solution was obtained.

[0025] To the clear solution of L-Thyroxine Na in glycerol/water, Nipagin M Sodium (sodium methylparaben) was added while stirring until a clear solution was obtained. The remaining amount of glycerol was subsequently added until a clear solution was obtained.

[0026] After that, the pH of the solution was adjusted to approximately 5.5 by adding citric acid, and the volume was adjusted to the predetermined L-thyroxine concentration by adding minor amounts water. The final solution was filtered over a 1 µm filter, and filled in light-protective containers, such as amber type III glass 100 ml bottles sealed with child resistant, tamper evident screw caps.

[0027] Preferably, the doses of levothyroxine are packed in dose units or monodose delivery sytems of the levothyroxine solution. Such systems comprise sealed vessels holding dosed units mentioned above. The vessels are made for instance of PVC or PVDC or composite materials comprising plastic materials reinforced with alluminium and/or glass layers for a better protection from are and/or light. These vessels are appropiate for pharmaceutical use and have volumes from 1 up to 10 ml capable to deliver doses from 25µg up to 300 µg of levothyroxine Na. The vessels may have the form of an ampoule, sachet, vial, blister pack, tube, or a stick pack made from plastic or glass.

[0028] Oral solutions of different concentrations may be obtained using the method described above. The amounts of ingredients are shown in the tables below for solutions containing 5 µg/ml (25 µg in 5 ml), 10 µg/ml (50 µg in 5 ml), and 20 µg/ml (100 µg in 5 ml). The method above may be scaled up or down using techniques known in the art to obtain different quantities and/or concentrations.
Table I: 25 mg dose

COMPOSITION IN ACTIVE SUBSTANCE(S)					
N O	NAME OF INGREDIENTS	FUNCTION	REFERENCE STANDARDS	QUANTITY	UNITS
1.	LEVOTHYROXINE SODIUM	Active ingredient	Ph. Eur.	25.00	MCG
COMPOSITION IN EXCIPIENTS AND OTHER INGREDIENTS					
No	NAME OF INGREDIENTS	FUNCTION	REFERENCE STANDARDS	QUANTITY	UNITS
1.	GLYCEROL liquid	Dissolving agent	Ph.Eur.	2-4	G
2.	CITRIC ACID	Buffering agent	Ph. Eur.	qs to pH 5.5	MG
3.	NIPAGIN M sodium	Antimicrobial agent	Ph.Eur.	0.002-0.009	G
4.	PURIFIED WATER	Solvent	Ph.Eur.	qs to 5 ml (about 2.00 gr)	G
5.	SODIUM HYDROXIDE 1N	pH adjustment	Ph.Eur.	qs to pH 10	MG
TOTAL QUANTITY				5.00	ML

Table II: 50mg dose

COMPOSITION IN ACTIVE SUBSTANCE(S)					
No	NAME OF INGREDIENTS	FUNCTION	REFERENCE STANDARDS	QUANTITY	UNITS
1.	LEVOTHYROXINE SODIUM	Active ingredient	Ph.Eur.	50.00	MCG
COMPOSITION IN EXCIPIENTS AND OTHER INGREDIENTS					
No	NAME OF INGREDIENTS	FUNCTION	REFERENCE STANDARDS	QUANTITY	UNITS
1.	GLYCEROL liquid	Dissolving agent	Ph.Eur.	2-4	G
2.	CITRIC ACID	Buffering agent	Ph.Eur.	qs to pH 5.5	MG
3.	NIPAGIN M sodium	Antimicrobial agent	Ph.Eur.	0.002-0.009	G
4.	PURIFIED WATER	Solvent	Ph.Eur.	qs to 5 ml (about 2.00 gr)	G
5.	SODIUM HYDROXIDE 1N	pH adjustment	Ph.Eur.	qs to pH 10	MG
TOTAL QUANTITY				5.00	ML

Table III: 100mg dose

COMPOSITION IN ACTIVE SUBSTANCE(S)				
NAME OF INGREDIENTS	**FUNCTION**	**REFERENCE STANDARDS**	**QUANTITY**	**UNITS**
LEVOTHYROXINE SODIUM	**Active ingredient**	**Ph.Eur.**	**100.00**	**MCG**

COMPOSITION IN EXCIPIENTS AND OTHER INGREDIENTS					
No	**NAME OF INGREDIENTS**	**FUNCTION**	**REFERENCE STANDARDS**	**QUANTITY**	**UNITS**
1.	GLYCEROL liquid	Dissolving agent	Ph.Eur.	2-4	**G**
2.	CITRIC ACID	Buffering agent	Ph.Eur.	qs to pH 5.5	**MG**
3.	NIPAGIN M sodium	Antimicrobial agent	Ph.Eur.	0.002-0.009	**G**

COMPOSITION IN EXCIPIENTS AND OTHER INGREDIENTS					
No	**NAME OF INGREDIENTS**	**FUNCTION**	**REFERENCE STANDARDS**	**QUANTITY**	**UNITS**
4.	PURIFIED WATER	Solvent	Ph.Eur.	qs to 5 ml (about 2.00 gr)	**G**
5.	SODIUM HYDROXIDE 1N	pH adjustment	Ph.Eur.	qs to pH 10	**MG**
TOTAL QUANTITY				**5.00**	**ML**

Comparative tests:

[0029] The stability of the solutions according to the invention was tested against commercially available levothyroxine solutions prepared using the same ingredients as mentioned in the tables above, differing only in their method of preparation. These commercially available solutions are sold under the brand name Evotrox. Analytical results are shown in table IV.

Table IV:

Test	Method	Results		
		BATCHES OF EVOTROX® ORAL SOLUTION		
		25 mcg/5ml	50 mcg/5ml	100 mcg/ 5ml
General items		Lot No : EVT 010	Lot No : EVR 012	Lot No : EVX 011
• Appearance	Visual examination	amber glass bottle with cap containing a clear viscous liquid*		
• Clarity and degree of opalescence of liquids	Ph.Eur.cur.ed .(2.2.1)	clear viscous liquid		
• pH value	Ph.Eur.cur.ed . (2.2.3)	5.6	5.6	5.6
• Relative density	Ph.Eur.cur.ed . (2.2.5)	1.1	1.1	1.1
Identity - Assay				
• Identification	Ph.Eur.cur.ed . (2.2.29)			
Levothyroxine sodium (HPLC)		Retention time complies with RS	Retention time complies with RS	Reten tion time comp lies with RS
Sodium methyl paraben (E219)		Retention time complies with RS	Retention time complies with RS	Reten tion time comp lies with RS
• Assay	Ph.Eur.cur.ed .(2.2.29)			
- Levothyroxine sodium (HPLC)		77.2 %	78.9 %	84.0 %
Purity tests				
• Related substance				
- Liothyronine	NMT 1.00%	1.4 %	Not performed	1.40 %
- Single unknown impurities	NMT 1.00%	10.4 %	Not performed	1.5 %
- Total impurities	NMT 1.00%	16.2 %	Not performed	3.0 %

[0030] Before the tests, all solutions were tested for purity using HPLC. Comparative tests of the pure compositions according to the invention and the EVOTROX solutions were done under normal controlled and stress conditions.

[0031] Table V shows the results for the Evotrox solutions:

Table V: 25 µg/5ml solutions stability

• after 1 month forced studies	RESULTS		
Conditions	normal	40°C	70°C
Appearance	Clear viscous solution with floating particles in some samples*		
pH	5.5		
Assay	77.2%	-	-
Liothyronine	1.4%	-	-
Major unspecified impurity	10.4%	-	-
Total unspecified impurities	16.2%	-	-
Glycerol	~500 g /L		
Package	Brown glass bottles holding 100 ml of solution		
* most of the evotrox® samples had floating particles even before we placed them for pre-stability studies in the oven.			
	Test and results of Evotrox® 25 microgram / 5ml Oral Solution		

Table VI: Test and results of Evotrox® 100 microgram / 5ml Oral Solution

• after 1 month forced studies	RESULTS		
Conditions	normal	40°C	70°C
Appearance	Clear viscous solution with floating particles in some samples*		
Assay	84.0%	73.4 %	-
Liothyronine	1.4%	4.8%	-
Major unspecified impurity	1.5%	3.4%	-
Total unspecified impurities	3.0%	5.4%	-
Glycerol	~500 g /L		
Package	Brown glass bottles holding 100 ml of solution		
* most of the evotrox® samples had floating particles even before we placed them for pre-stability studies in the oven.			
	Test and results of Evotrox® 100 microgram / 5ml Oral Solution		

Table: 100 µg/5ml solutions

PARAMETERS	PHARMA-DATA 100 MCG/5ML		Evotrox® EVX011	
• after 2 months forced studies	normal	40°C	normal	40°C
Appearance	clear solution		Almost clear	
Final pH	5.5		5.6	
Assay	106.4%	104.4%	85.2%	73.4%
Liothyronine	0.19%	0.77%	0.81%	4.8%
Any unspecified impurity	0.12%	0.8%	1.4%	3.4%
Total other unspecified impurities	0.28%	1.1%	3.4%	5.4%
• after 6 months forced studies	normal	40°C	normal	40°C
Appearance	clear solution		Almost clear	
Final pH	5.5		5.6	
Assay	103.9%	99.1%	80.8%	65.8%
Liothyronine	0.16%	2.4%	1.6%	6.5%
Any unspecified impurity	0.07%	0.34%	1.3%	9.6%
Total other unspecified impurities	0.35%	0.65%	3.8%	11.2%

[0032] In both the 25 µg/5ml and 100 µg/5ml solutions, the levothyroxine solutions prepared using the method according to the invention show significantly less impurities after 2 months under normal or stress conditions. Thus it is concluded the solutions prepared according to the invention have a higher stability during storage, even though the constituents of the starting solutions were virtually the same according to HPLC analysis.

Patentkrav

1. Fremgangsmåde til fremstilling af en oral levothyroxinsammensætning, hvilken fremgangsmåde omfatter trinnene:
a) at tilvejebringe et salt af levothyroxin, fortrinsvis natriumsaltet af levothyroxin
b) at blande levothyroxin med et vandigt opløsningsmiddel, hvor det vandige opløsningsmiddel er en blanding af vand og et vandblandbart organisk opløsningsmiddel, hvor det vandblandbare organiske opløsningsmiddel omfatter glycerol,
c) at justere pH'en til en pH på mindst 8 for at frembringe et basisk vandigt opløsningsmiddel og
d) at opløse levothyroxinet i det basiske vandige opløsningsmiddel for at frembringe en levothyroxinopløsning og
e) at sænke pH'en af levothyroxinopløsningen til mellem 5-6.

2. Fremgangsmåde ifølge krav 1, hvorved pH'en sænkes til 5,5 i trin e).

3. Fremgangsmåde ifølge krav 1 eller 2, hvorved pH'en justeres fra 9 til 11 i trin c).

4. Fremgangsmåde ifølge krav 3, hvorved pH'en justeres til 10 i trin c).

5. Fremgangsmåde ifølge et af de foregående krav, hvorved justeringen af pH'en blev foretaget ved tilsætning af en base.

6. Fremgangsmåde ifølge krav 5, hvorved den tilsatte base er en natriumhydroxidopløsning.

7. Fremgangsmåde ifølge et af de foregående krav, hvorved justeringen af pH'en i trin e) blev foretaget ved anvendelse af en carboxylsyre.

8. Fremgangsmåde ifølge krav 7, hvorved carboxylsyren er citronsyre.

9. Fremgangsmåde ifølge et af de foregående krav, hvorved i trin b) levothyroxinet blandes med det vandige opløsningsmiddel, mens blandingen opvarmes til 30-70° C, fortrinsvis fra 40-50 °C, mere fortrinsvis fra 40-45° C.

10. Fremgangsmåde ifølge et af de foregående krav, hvorved der også tilsættes et konserveringsmiddel til det vandige opløsningsmiddel.

11. Fremgangsmåde ifølge krav 10, hvorved konserveringsmidlet er natriummethylparaben.

12. Oral levothyroxinsammensætning, der kan opnås ved anvendelse af fremgangsmåden ifølge et af de foregående krav

13. Oral levothyroxinsammensætning ifølge krav 12, hvor sammensætningen omfatter en natriumlevothyroxinkoncentration på ca. 25 µg i 5 ml, ca. 50 µg i 5 ml eller ca. 100 µg i 5 ml, hvor sammensætningen omfatter natriumlevothyroxin, glycerol, vand og et konserveringsmiddel.

14. Oral levothyroxinsammensætning ifølge et af kravene 12 eller 13, hvor sammensætningen er pakket i et enhedsdosissystem udvalgt fra gruppen bestående af ampuller, sachets, vial's blisterpakninger, rør eller stick packs, hvor enhedsdosen er indrettet til at afgive separate doser af levothyroxin fra 25 op til 300 mcg per enkeltdosis.