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Eljárás levotiroxin-oldat előállítására

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(54) **METHOD FOR THE PREPARATION OF A LEVOTHYROXINE SOLUTION**

HERSTELLUNGSMETHODE FÜR EINE LEVOTHYROXINLÖSUNG

MÉTHODE DE MANUFACTURE D'UNE SOLUTION DE LÉVOTHYROXINE

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- **CHONG MIN WON: "Kinetics of Degradation of Levothyroxine in Aqueous Solution and in Solid State", PHARMACEUTICAL RESEARCH, vol. 9, no. 1, 1991, pages 131-137, XP9156943,**

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Description

FIELD OF THE INVENTION

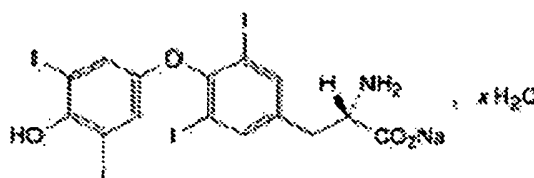
[0001] The invention relates to a method for the preparation of an oral levothyroxine composition.

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 advantage 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:

- a) providing a salt of levothyroxine, preferably the sodium salt of levothyroxine
- 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,
- c) adjusting the pH to a pH of at least 8 to yield a basic aqueous solvent, and
- d) dissolving the levothyroxine in the basic aqueous solvent to yield a levothyroxine solution, and
- 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 levothyroxine 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 Lauric 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 yields 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, vials, 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 systems 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 aluminium and/or glass layers for a better protection from air and/or light. These vessels are appropriate for pharmaceutical use and have volumes from 1 up to 10 ml capable to deliver doses from 25 µg 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

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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
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 prep-

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aration. 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	LotNo : 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	Retention time complies with RS
Sodium methyl paraben (E219)		Retention time complies with RS	Retention time complies with RS	Retention time complies 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		
	normal	40°C	70°C
Conditions			
Appearance	Clear viscous solution with floating particles in some samples*		
pH	5.5		
Assay	77.2%	-	-
Liothyronine	1.4%	-	-
Major unspecified impurity	10.4%	-	-

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(continued)

• after 1 month forced studies	RESULTS		
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

35	PARAMETERS	PHARMA-DATA 100 MCG/5ML		Evotrox® EVX011	
	• after 2 months forced studies	normal	40°C	normal	40°C
40	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%
45	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	
50	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%
55	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.

Claims

1. Method for the preparation of an oral levothyroxine composition, comprising the steps of:
 - a) providing a salt of levothyroxine, preferably the sodium salt of levothyroxine
 - 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,
 - c) adjusting the pH to a pH of at least 8 to yield a basic aqueous solvent, and
 - d) dissolving the levothyroxine in the basic aqueous solvent to yield a levothyroxine solution, and
 - e) lowering the pH of the levothyroxine solution to between 5-6.
2. Method according to claim 1, where in step e) the pH is lowered to 5.5.
3. Method according to claim 1 or 2, where in step c) the pH is adjusted to from 9 to 11.
4. Method of claim 3, where in step c) the pH is adjusted to 10.
5. Method according to any of the preceding claims, wherein the adjusting of the pH was done by adding a base.
6. Method according to claim 5, wherein the added base is a sodium hydroxide solution.
7. Method according to any of the preceding claims, wherein the adjusting of the pH in step e) was done using a carboxylic acid.
8. Method according to claim 7, wherein the carboxylic acid is citric acid.
9. Method according to any of the preceding claims, where 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.
10. Method according to any of the preceding claims, wherein also a preservative is added to the aqueous solvent.
11. Method according to claim 10, wherein the preservative is sodium methylparaben.
12. Oral Levothyroxine composition obtainable using the method according to any of the preceding claims.
13. Oral Levothyroxine composition according to claim 12, wherein 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, wherein the composition comprises sodium levothyroxine, glycerol, water and a preservative.
14. Oral Levothyroxine composition according to any of the claims 12 or 13, wherein the 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.

Patentansprüche

1. Verfahren zur Herstellung einer oralen Levothyroxin-Zusammensetzung, das folgende Schritte umfasst:
 - a) Bereitstellen eines Salzes von Levothyroxin, vorzugsweise des Natriumsalzes von Levothyroxin,
 - b) Mischen von Levothyroxin mit einem wässrigen Lösungsmittel, wobei das wässrige Lösungsmittel ein Gemisch aus Wasser und einem mit Wasser mischbaren organischen Lösungsmittel ist, wobei das mit Wasser mischbare organische Lösungsmittel Glycerin umfasst,
 - c) Einstellen des pH-Wertes auf einen pH-Wert von mindestens 8 zur Erzeugung eines basischen wässrigen Lösungsmittels, und

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- d) Lösen des Levothyroxins in der basischen wässrigen Lösung zur Erzeugung einer Levothyroxin-Lösung, und
- e) Senken des pH-Wertes der Levothyroxin-Lösung auf 5 bis 6.

2. Verfahren nach Anspruch 1, bei dem in Schritt e) der pH-Wert auf 5,5 gesenkt wird.
3. Verfahren nach Anspruch 1 oder 2, bei dem in Schritt c) der pH-Wert auf 9 bis 11 eingestellt wird.
4. Verfahren nach Anspruch 3, bei dem in Schritt c) der pH-Wert auf 10 eingestellt wird.
5. Verfahren nach einem der vorangegangenen Ansprüche, bei dem die Einstellung des pH-Wertes durch Zugabe einer Base erfolgte.
6. Verfahren nach Anspruch 5, bei dem die zugegebene Base eine Natriumhydroxidlösung ist.
7. Verfahren nach einem der vorangegangenen Ansprüche, bei dem die Einstellung des pH-Wertes in Schritt e) mittels einer Carbonsäure erfolgte.
8. Verfahren nach Anspruch 7, bei dem die Carbonsäure Zitronensäure ist.
9. Verfahren nach einem der vorangegangenen Ansprüche, bei dem in Schritt b) Levothyroxin mit dem wässrigen Lösungsmittel während einer Erwärmung des Gemisches auf 30 bis 70 °C, vorzugsweise 40 bis 50 °C und noch bevorzugter 40 bis 45 °C gemischt wird.
10. Verfahren nach einem der vorangegangenen Ansprüche, bei dem dem wässrigen Lösungsmittel zudem ein Konservierungsmittel zugesetzt wird.
11. Verfahren nach Anspruch 10, bei dem das Konservierungsmittel Natriummethylparaben ist.
12. Orale Levothyroxin-Zusammensetzung, die unter Anwendung des Verfahrens nach einem der vorangegangenen Ansprüche erhältlich ist.
13. Orale Levothyroxin-Zusammensetzung nach Anspruch 12, wobei die Zusammensetzung eine Natriumlevothyroxin-Konzentration von etwa 25 µg in 5 ml, etwa 50 µg in 5 ml oder etwa 100 µg in 5 ml enthält und Natriumlevothyroxin, Glycerin, Wasser und ein Konservierungsmittel umfasst.
14. Orale Levothyroxin-Zusammensetzung nach Anspruch 12 oder 13, wobei die Zusammensetzung in einem Dosiereinheitensystem verpackt ist, das aus der Gruppe bestehend aus Ampullen, Sachets, Durchstechflaschen, Blisterpackungen, Röhrchen oder Stickpacks ausgewählt ist, wobei die Dosiereinheit so gestaltet ist, dass separate Levothyroxin-Dosen von 25 bis 300 µg pro Einzeldosis entnehmbar sind.

Revendications

1. Procédé de préparation d'une composition orale de lévothyroxine, comprenant les étapes de :
 - a) fourniture d'un sel de lévothyroxine, de préférence le sel de sodium de lévothyroxine,
 - b) mélange de la lévothyroxine avec un solvant aqueux, le solvant aqueux étant un mélange d'eau et d'un solvant organique miscible avec l'eau, le solvant organique miscible avec l'eau comprenant du glycérol,
 - c) ajustement du pH à un pH d'au moins 8 pour donner un solvant aqueux basique, et
 - d) dissolution de la lévothyroxine dans le solvant aqueux basique pour donner une solution de lévothyroxine, et
 - e) abaissement du pH de la solution de lévothyroxine jusqu'à une valeur comprise entre 5 et 6.
2. Procédé selon la revendication 1, dans lequel, dans l'étape e), le pH est abaissé jusqu'à 5,5.
3. Procédé selon la revendication 1 ou 2, dans lequel, dans l'étape c), le pH est ajusté à une valeur de 9 à 11.
4. Procédé selon la revendication 3, dans lequel, dans l'étape c), le pH est ajusté à 10.

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5. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'ajustement du pH a été réalisé par addition d'une base.
6. Procédé selon la revendication 5, dans lequel la base ajoutée est une solution d'hydroxyde de sodium.
7. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'ajustement du pH dans l'étape e) a été réalisé à l'aide d'un acide carboxylique.
8. Procédé selon la revendication 7, dans lequel l'acide carboxylique est l'acide citrique.
9. Procédé selon l'une quelconque des revendications précédentes, dans lequel, dans l'étape b), la lévothyroxine est mélangée avec le solvant aqueux sous chauffage du mélange à une température de 30 à 70°C, de préférence de 40 à 50°C, de manière davantage préférée de 40 à 45°C.
10. Procédé selon l'une quelconque des revendications précédentes, dans lequel un conservateur est également ajouté au solvant aqueux.
11. Procédé selon la revendication 10, dans lequel le conservateur est le méthylparabène de sodium.
12. Composition orale de lévothyroxine susceptible d'être obtenue par le procédé selon l'une quelconque des revendications précédentes.
13. Composition orale de lévothyroxine selon la revendication 12, dans laquelle la composition a une concentration de lévothyroxine de sodium d'environ 25 µg dans 5 ml, d'environ 50 µg dans 5 ml ou d'environ 100 µg dans 5 ml, dans laquelle la composition comprend de la lévothyroxine de sodium, du glycérol, de l'eau et un conservateur.
14. Composition orale de lévothyroxine selon l'une quelconque des revendications 12 ou 13, dans laquelle la composition est emballée dans un système de dose unitaire choisi dans le groupe constitué des ampoules, des sachets, des plaquettes pour fioles, des tubes ou des bâtonnets, dans laquelle la dose unitaire est conçue pour délivrer des doses séparées de lévothyroxine de 25 jusqu'à 300 mcg par dose unique.

Eljárás levotiroxin-oldat előállítására

SZABADALMI IGÉNYPONTOK

1. Eljárás orális levotiroxin készítmény előállítására, mely eljárás a következő lépéseket tartalmazza:

- a) levotiroxin sôt, elönyösen levotiroxin nátriumsôt biztosítunk,
- b) a levotiroxint egy vizes oldószerrel keverjük, a vizes oldószer víz és vízzel elegyedő szerves oldószer keveréke, a vízzel elegyedő szerves oldószer glicerint tartalmaz,
- c) a pH értéket beállítjuk, legalább 8-as pH értékre, bázikus vizes oldat előállítására,
- d) a levotiroxint a bázikus vizes oldatban oldjuk levotiroxin-oldat előállítására, és
- e) a levotiroxin oldat pH értékét 5-6 közé csökkentjük.

2. Az 1. igénypont szerinti eljárás, ahol a b) lépésben a pH értéket 5,5-re csökkentjük.

3. Az 1. vagy 2. igénypont szerinti eljárás, ahol a c) lépésben a pH értéket 9-11-re állítjuk be.

4. A 3. igénypont szerinti eljárás, ahol a c) lépésben a pH értéket 10-re állítjuk be.

5. Az előző igénypontok bármelyike szerinti eljárás, ahol a pH-érték beállítását bázis adagolásával végeztük.

6. A 6. igénypont szerinti eljárás, ahol a hozzáadott bázis nátriumhidroxid-oldat.

7. Az előző igénypontok bármelyike szerinti eljárás, ahol a pH beállítását az e) lépésben karbonsav alkalmazásával végeztük.

8. A 7. igénypont szerinti eljárás, ahol a karbonsav citromsav.

9. Az előző igénypontok bármelyike szerinti eljárás, ahol a b) lépésben a levotiroxint a vizes oldószerrel az elegy 30-70 °C hőmérsékletre, elönyösen 40-50 °C hőmérsékletre, még elönyösebben 40-45 °C hőmérsékletre való melegítése közben keverjük össze.

10. Az előző igénypontok bármelyike szerinti eljárás, ahol a vizes oldószerhez konzerválószer is adunk.

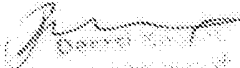
11. A 10. igénypont szerinti eljárás, ahol a konzerválószer nátrium-metilparaben.

12. Az előző igénypontok bármelyike szerinti eljárással előállítható orális levotiroxin kompozíció.

13. A 12. igénypont szerinti orális levotiroxin kompozíció, ahol a kompozíció 5 ml-e körülbelül 25 µg koncentrációban, 5 ml-e körülbelül 50 µg koncentrációban, vagy 5 ml-e körülbelül 100 µg koncentrációban tartalmaz levotiroxin-nátriumot, és ahol a kompozíció levotiroxin-nátriumot, glicerint, vizet és konzerválószeret tartalmaz.

14. A 12. vagy 13. igénypontok bármelyike szerinti orális levotiroxin kompozíció, ahol a kompozíció az ampulla, tasak, flóla buborék csomagolás, cső vagy pálcika csomag csoportból választott egységdózis rendszerben van csomagolva, ahol az egységdózis úgy van kialakítva, hogy különálló 25 – 300 mcg/egységdózis levotiroxin dózisok szabadulnak fel.

A meghatalmazott


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