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STABLE LIQUID ORAL DOSAGE FORMS OF LIOTHYRONINE

FIELD OF THE INVENTION

The present invention relates to stable liquid oral dosage forms of liothyronine, including methods for making the liquid oral dosage forms, packaging and storing the liquid oral dosage forms and methods for administering the liquid oral dosage forms.

BACKGROUND OF THE INVENTION

Liothyronine sodium (L-triiodothyronine or LT_3) is a synthetic form of a thyroid hormone liothyronine in sodium salt form. Liothyronine sodium is currently available as tablet dosage form commercially available under the tradename CYTOMEL® indicated for: (1) replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism; 2) adjunct to surgery and radioiodine therapy in the management of well-differentiated thyroid cancer, and 3) as a diagnostic agent in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy. Liothyronine sodium is also available as injectable dosage form under the tradename TRIOSTAT® indicated in the treatment of myxedema coma/precoma and can be used in patients allergic to desiccated thyroid or thyroid extract derived from pork or beef.

Liquid oral dosage forms of liothyronine sodium will have the advantages of ease of administration (easy to swallow), and will offer a significant advantage over tablet dosage forms in terms of dose adjustments and titrations during the course of the therapy. To date, there are no approved liquid oral dosage forms of liothyronine sodium.

Therefore, an objective of this invention is a stable liquid dosage form for oral administration.

SUMMARY OF THE INVENSION

The present invention is a stable liquid oral dosage form comprising liothyronine, water, at least one buffering agent and a solvent. The liquid oral dosage form may also comprise one or more antimicrobial agents, preservatives and pH adjusting agents. In certain embodiments the pH of the liquid oral dosage form ranges from about 3.0-6.5, preferably about 3.5-6.0 and more preferably about 4.0-5.5. The liquid oral dosage forms of the present invention may also further

comprise one or more additional pharmaceutical acceptable excipients such as flavoring agents, chelating agents, viscosity enhancing agents, solubility enhancing agents, coloring agents or combinations thereof.

In some embodiments the liothyronine will be present in liquid oral dosage forms in a concentration range of about 0.1 µg/mL to about 200 µg/mL, preferably from about 0.5 µg/mL to about 100 µg/mL and most preferably about 1 µg/mL to about 50 µg/mL.

The liquid oral dosage forms of the present invention may be packaged and stored in pharmaceutically acceptable containers such as glass bottles, vials and/or ampoules or plastic bottles, vials, and/or ampoules. Representative containers are described in U.S. Patent Nos. 9,050,307; 10,537,538 and 6,706,255, which are incorporated herein by reference. In certain embodiments, the liquid oral dosage form is stored in amber glass or amber polyethylene terephthalate ("PET") bottles that are sealed with an appropriate cap.

The liquid oral dosage forms should remain stable for 3-30 months when stored at room temperature, in inverted and upright orientations. The liquid oral dosage forms should also remain stable under freeze thaw testing for at least 2 or more freeze thaw cycles. The liquid oral dosage forms should also remain stable for 0.5-6 months under accelerated storage conditions such as elevated temperatures and humidity.

The present invention also includes a method for making the stable liquid oral dosage form.

DETAILED DESCRIPTION

Before the present invention is further described, it is to be understood that this invention is not limited to the particular embodiments described. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It should be noted that as used herein, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise.

The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable, i.e. without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

The term "therapeutically effective amount" means an amount effective to deliver a therapeutically effective amount of an active agent needed to delay the onset of, inhibit the progression of, or halt altogether the particular disease, disorder or condition being treated, or to otherwise provide the desired effect on the subject to be treated. As one of ordinary skill in the art would understand, a therapeutically effective amount varies with the patient's age, condition, and gender, as well as the nature and extent of the disease, disorder or condition in the patient, and the dosage may be adjusted by the individual physician (or veterinarian).

The terms "treating" and "treatment" refer to reversing, alleviating, inhibiting, or slowing the progress of the disease, disorder, or condition to which such terms apply, or one or more symptoms of such disease, disorder, or condition.

The term “subject” or “patient” used herein refers to a human patient or a mammalian animal, such as cat, dog, cow, horse, monkey, or the like.

As disclosed herein, a number of ranges of values are provided. It is understood that each intervening value, to the tenth of the unit of the lower limit, unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither, or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

As used herein, the term “normal storage conditions” refers to storage at room temperature, approximately 25°C and approximately 60% relative humidity for at least three months or longer, preferably at least six months or longer, more preferably at least one year or longer and most preferably at least two years or longer. The dosage form in accordance with the present invention should be stored in pharmaceutically acceptable containers such as glass bottles, vials and/or ampoules or plastic bottles, vials, and/or ampoules.

As used herein, the term “accelerated storage conditions” refers to storage at approximately 40°C and approximately 75% relative humidity for at least two weeks or longer, one month or longer, two months or longer, three months or longer, four months or longer, five

months or longer, or six months or longer. The dosage form in accordance with the present invention should be stored in pharmaceutically acceptable containers such as such as glass bottles, vials and/or ampoules or plastic bottles, vials, and/or ampoules.

The terms "comprising," "having," "including," and "containing," or the like, are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted.

The liquid oral dosage forms described herein are useful in the treatment of disorders associated with improvement of the thyroid hormone function in animals including human beings for example, myxedema, cretinism or obesity. The liothyronine can be prepared synthetically or can be isolated directly from the thyroid gland of animals.

The liothyronine used in the present liquid oral dosage forms may be a free base or salt and exist as one or more polymorphic or solvate forms (for example one or more crystalline forms, amorphous forms, phases, solid solutions and/or mixtures thereof).

The liquid oral dosages forms of the present invention will comprise liothyronine, water, at least one buffering agent to maintain the pH of the liquid oral dosage form within the target pH range during storage; a solvent and optionally one or more pharmaceutically acceptable excipients such as antimicrobial agents, preservatives, pH adjusting agents; flavoring agents, chelating agents, viscosity enhancing agents, solubility enhancing agents, coloring agents or combinations thereof.

Examples of buffer agents that may be used in the present invention include but are not limited to acetic acid, adipic acid, ammonium carbonate, ammonium phosphate, boric acid, citric acid, lactic acid, phosphoric acid, potassium citrate, potassium metaphosphate, potassium phosphate, sodium acetate, sodium citrate, sodium lactate, sodium phosphate, succinic acid and mixtures thereof. The amount of buffer can be easily determined by reference to conventional pharmaceutical reference books such as Remington's The Science and Practice of Pharmacy, 21st ed. (2005) and the Handbook of Pharmaceutical Excipients, 5th ed. (2006).

Examples of antimicrobial agents and preservatives that may be used in the present invention include, but are not limited to, edetic acid and their alkali salts such as disodium EDTA and calcium EDTA, benzyl alcohol, methylparaben, propylparaben, butylparaben, chlorobutanol, phenylethyl alcohol, benzalkonium chloride, thimerosal, propylene glycol, sorbic acid, and benzoic acid derivatives.

Examples of solvents that may be used in the present invention include but are not limited to aliphatic mono- and polyvalent alcohols which contain 2-6 carbon atoms (including, but not limited to, ethanol, 1,2-propylene glycol, sorbitol, and glycerin), polyglycols such as polyethylene glycols, oils such as cottonseed, peanut, or corn oils and combinations thereof. In certain embodiments, the solvent is ethanol, glycerin or a combination of glycerin and ethanol. In certain embodiments, the liquid oral dosage form is free of ethanol.

Examples of pH adjusting agents that may be used in the present invention include, but are not limited to, any of the pharmaceutically acceptable acids or bases used to adjust the pH of pharmaceutical compositions. Examples of compounds typically used to adjust the pH of pharmaceutical compositions include hydrochloric acid, citric acid, lactic acid, tartaric acid, glacial acetic acid, sodium hydroxide, potassium hydroxide, arginine, lysine, meglumine, triethanol amine, or combinations thereof.

Examples of flavoring agents that may be used in the present invention include but are not limited to artificial sweeteners such as aspartame, saccharin, sucralose, dipotassium glycyrrhizinate, stevia, thaumatin and flavorants such as citric acid, peppermint oil, wintergreen oil, menthol, lemon, lime, orange, grape, cherry and vanilla extract. Additional flavoring agents, (aka taste enhancing agents) are described in U.S. Patent No. 6,027,746 and are incorporated herein by reference.

Examples of chelating agents that may be used in the present invention include but are not limited to ethylenediaminetetraacetic acid (EDTA) and its derivatives, thioglycolic acid, thiolactic acid, thioglycerol and the like.

Examples of viscosity enhancing agents that may be used in the present invention include but are not limited to waxes, clays, gums, microcrystalline cellulose, magnesium aluminum silicate, bentonite, agar-agar, hypromellose, sodium carboxymethyl cellulose, carbopol/carbomer, pectin, acacia, tragacanth, polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, ethylcellulose, polyacrylates, polyox and combination of the foregoing.

Examples of solubility enhancing agents that may be used in the present invention include but are not limited to surfactants (ionic surfactants and nonionic surfactants), polysorbates, derivatives of tocopherol, poloxamers, monoglycerides, diglycerides, fatty acids, fatty alcohols and mixtures thereof. A more complete listing of solubility enhancing agents can be found on

page 3258 of the United States Pharmacopeia 29 (2006) which is incorporated herein by reference. The solubility enhancing agent may also include a cyclodextrin.

The liquid oral dosage forms of the present invention are stable when prepared and stored under normal and accelerated conditions. More specifically, the liquid oral dosage forms of the present invention will contain about 1.0% or less of any individual liothyronine degradation product or impurity, preferably about 0.75% or less of any individual degradation product or impurity, and most preferably about 0.5% or less of any individual degradation product or impurity when the liquid dosage form is stored in a sealed bottle, preferably a sealed glass or plastic bottle, at approximately 25°C and approximately 60% relative humidity for at least three months, preferably at least six months and most preferably at least one year and/or at approximately 40°C and approximately 75% relative humidity for one month, two months, or three months.

The liquid oral dosage forms of the present invention should also contain a total amount of liothyronine degradation products and/or impurities of about 2.0% or less, preferably about 1.5% or less, and most preferably about 1.0% or less when the liquid oral dosage form is stored in a sealed bottle, preferably a sealed glass or plastic bottle at approximately 25°C and approximately 60% relative humidity for at least three months, preferably at least six months, and most preferably at least one year and/or at approximately 40°C and approximately 75% relative humidity for one month, two months, or three months.

The liquid oral dosage forms of the present invention should also maintain 90%-110%, preferably 95%-105% of the labeled amount of liothyronine when the liquid oral dosage form is stored in a sealed bottle, preferably a sealed glass or plastic bottle at: (i) approximately 25°C and approximately 60% relative humidity for at least three months, preferably at least six months and most preferably at least one year; (ii) approximately 40°C and approximately 75% relative humidity for one month, two months, or three months and/or a combination of (i) and (ii).

The pH of the liquid oral dosage forms of the present invention should also be ± 0.75 of the target pH, preferably ± 0.5 of the target pH and most preferably ±0.25 of the target pH when the liquid oral dosage form is stored in a sealed bottle, preferably a sealed glass or plastic bottle at: (i) approximately 25°C and approximately 60% relative humidity for at least three months, preferably at least six months and most preferably at least one year; (ii) approximately 40°C and

approximately 75% relative humidity for one month, two months, or three months and/or a combination of (i) and (ii).

Certain embodiments of the liothyronine liquid dosage forms will comprise about 0.1 µg/mL to about 200 µg/mL, preferably from about 0.5 µg/mL to about 100 µg/mL and most preferably about 1 µg/mL to about 50 µg/mL of liothyronine or a pharmaceutically acceptable salt thereof and the excipients as recited in the following tables:

	Preferred	**More Preferred**	**Most Preferred**
Buffer	0-15 mg	0.01-12 mg	0.05-10 mg
Preservative	0-10 mg	0.005-7.5 mg	0.01- 5 mg
Solvent	200-800 mg	300-700 mg	400-600 mg
pH Adjusting Agent	QS to a pH of 3.0 to 6	QS to a pH of 3.5 to 5.75	QS to a pH of 3.75 to 5.5
Purified Water QS to	1 mL (100%)	1 mL	1 mL

	Preferred	**More Preferred**	**Most Preferred**
Buffer	0.0-1.5% w/v	0.001-1.2% w/v	0.005-1.0% w/v
Preservative	0.0-1.0% w/v	0.0005-0.75% w/v	0.001-0.5% w/v
Solvent	20.0-80.0% w/v	30.0-70.0% w/v	40.0-60.0% w/v
pH Adjusting Agent	QS to a pH of 3.0 to 6	QS to a pH of 3.5 to 5.75	QS to a pH of 3.75 to 5.5
Purified Water QS to	1 mL (100%)	1 mL	1 mL

The buffer is preferably a phosphate or citrate buffer, such as a combination of a citrate salt, i.e. sodium or potassium citrate and citric acid or a phosphate salt such as a combination of mono- and dibasic sodium phosphate, or combinations of the foregoing.

The solvent is preferably a mono-alcohol (i.e., only one OH moiety) or a poly-alcohol (i.e., more than one OH moiety) which contain 2-6 carbon atoms, such as ethanol, 1,2-propylene glycol, sorbitol, and glycerin. In preferred embodiments the liothyronine liquid dosage forms are free of mono-alcohols such as ethanol.

The preservative is preferably benzyl alcohol, methylparaben, propylparaben, butylparaben, sorbic acid, benzoic acid and their alkali salts such as methylparaben sodium, and combinations of the foregoing.

The present invention also relates to a method for preparing a stable liothyronine liquid oral dosage form. The method comprises;

(i) preparing a first solution comprising water, buffer, solvent, and optionally other pharmaceutically acceptable excipients such as antimicrobial agents, preservatives, flavoring agents, chelating agents, viscosity enhancing agents, solubility enhancing agents, coloring agents or combinations wherein the first solution is at least about 1%, 2%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22% 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30% of a final manufacturing batch volume or any range thereof and wherein the first solution has a pH between about 3.5 to about 6.5, preferably about 3.75 to about 6.0.

(ii) adding a desired amount of liothyronine or pharmaceutically acceptable salt thereof to the first solution and mixing to obtain a liothyronine concentrate premix solution;

(iii) adding the liothyronine concentrate premix solution to a second solution having the same composition as the first solution only the second solution has a larger volume than the first solution and mixing to obtain a liothyronine third solution;

(iv) optionally adding water to the liothyronine third solution to obtain a final manufacturing batch volume if necessary so that the final manufacturing batch volume comprise about 0.1 µg/mL to about 200 µg/mL, preferably from about 0.5 µg/mL to about 100 µg/mL and most preferably about 1 µg/mL to about 50 µg/mL of liothyronine or a pharmaceutically acceptable salt;

(v) packaging the liothyronine liquid dosage form prepared in steps (iii) or (iv) into single or multiple dose containers for distribution to hospitals, pharmacies and/or patients.

The foregoing method may further comprise a step of adjusting the pH of the composition prepared in steps (i) to (iv) to the target pH of about 3.5 to about 6.5, preferably about 3.75 to about 5.5 and more preferably about 4.0 to about 5.0. The pH may be adjusted to the target pH by adding a pH adjusting agent as previously described such as NaOH or HCl.

The second solution of step (iii) may be slightly larger than the volume of the first solution, i.e., about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or greater than the volume of the

first solution. The volume of the second solution may be about 2 to about 50 times greater than the volume of the first solution, preferably about 5 to about 40 times greater than the first solution and more preferably about 10 to about 30 times greater than the first solution. For example if the first solution is 50 L, the second solution may be 1,000 mL (i.e., 20 times the first).

In certain embodiments of the present invention, the method for preparing the liothyronine liquid dosage form may comprise the following steps:

(ai) preparing a first solution comprising water, solvent, and a buffer in a first container;

(aii) placing a portion of the first solution in a second container, wherein the portion comprise 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2% or 1% by weight or volume of the total weight or volume of the first solution or any range thereof forming a second solution;

(aiii) combining the liothyronine or pharmaceutically acceptable salt thereof and the second solution to form a third solution;

(aiv) adding the third solution to the first solution and mixing to obtain a fourth solution.

The pH of the fourth solution may be adjusted to the target pH using a pH adjusting agent if necessary. Water, and optionally additional solvent, may be added to the fourth solution to adjust the final manufacturing batch volume and liothyronine concentration as previously described before packaging for distribution.

Other pharmaceutically acceptable excipients such as antimicrobial agents, preservatives, flavoring agents, chelating agents, viscosity enhancing agents, solubility enhancing agents, coloring agents or combinations thereof may be added at step (i) to (iv) or at a separate processing step.

In one embodiment of the foregoing methods for preparing the liothyronine liquid dosage forms of the present invention, an antimicrobial agent or preservative is added to the first solution of step (i); the second solution of step (aii) or the third solution of step (aiii).

In certain aspects of the present method, the liquid composition or solution to which the liothyronine or pharmaceutically acceptable salt thereof is added to or combined with should contain all the excipients that will be present in the final composition, with the exception of any pH adjusting agent.

In some embodiments of the foregoing methods the final manufacturing batch volume may range from about 250 L to about 5 L, preferably about 500 L to about 2,500 L and more preferably about 750 L to about 1,500 L.

The following Examples are provided by way of example only and are by no means intended to be limiting.

EXAMPLE 1

Numerous liothyronine liquid oral dosage forms have been prepared and their stability evaluated at accelerated conditions of 50°C and 40°C and at room temperature (RT) and refrigerated storage (2-8°C). The variables evaluated were:

(i) the effect of buffer type (citrate, phosphate);

(ii) the effect of pH (4.0, 5.0, 6.0, 7.0);

(iii) the effect of solvent type (glycerin, propylene glycol, PEG400);

(iv) the effect of glycerin concentration (20% v/v, 40% v/v, 60% v/v);

(v) the effect of solubility enhancing/complexing agent hydroxypropyl betacyclodexrrin (5% w/v, 10% w/v, 20% w/v); and

(vi) the effect of chelating agent edetate disodium.

The various liquid oral dosage forms are described in Tables 1-3 below.

Table 1 Composition of Liothyronine Sodium Oral Solution

Ingredients	Lot: PD-0021-007 mg/mL	Lot: PD-0021-010 mg/mL	Lot: PD-0021-013 mg/mL	Lot: PD-0021-016 mg/mL
Liothyronine sodium*	0.005169	0.005169	0.005169	0.005169
Citric acid Anhydrous	2.41	1.44	0.5103	0.0681
Sodium Citrate Dihydrate	2.2	3.68	5.1	5.78
Monobasic Sodium Phosphate Monohydrate	-	-	-	-
Dibasic Sodium Phosphate Heptahydrate	-	-	-	-
Methylparaben Sodium	1.8	1.8	1.8	1.8
Glycerin	504	504	504	504

Sodium Hydroxide Solution	QS	QS	QS	QS
Hydrochloric Acid Solution	QS	QS	QS	QS
pH	4	5	6	7
Purified Water QS to	1 mL	1 mL	1 mL	1 mL

Lots PD-0021-007 and PD0021-010 were packed in various configurations including amber glass bottles, amber PET bottles, clear glass bottles and white HDPE bottles. The bottles were sealed and stored at 5°C, 25°C, and 40°C for at least 3 months. After three months the liquid liothyronine oral solutions maintained 90%-110% of the original amount of liothyronine; maintained a target pH of 4 ± 0.5 and 5 ± 0.5 respectively; contained less than 0.75% of any individual liothyronine degradation product or impurity and less than 2.0% of a combined total amount of liothyronine degradation products and/or impurities (total amount of related substances).

Stability testing for Lots PD-0021-013 and PD-0021-016 were discontinued shortly after preparation due to the high amount of degradation products and/or impurities.

Table 2 Composition of Liothyronine Sodium Oral Solution

Ingredients	**Lot: PD-0021-019** **mg/mL**	**Lot: PD-0021-022** **mg/mL**	**Lot: PD-0021-025** **mg/mL**	**Lot: PD-0021-028** **mg/mL**
Liothyronine sodium*	0.005169	0.005169	0.005169	0.005169
Citric acid Anhydrous	-	-	-	-
Sodium Citrate Dihydrate	-	-	-	-
Monobasic Sodium Phosphate Monohydrate	2.7581	2.74	2.51	1.29
Dibasic Sodium Phosphate Heptahydrate	0.0034	0.04254	0.4913	2.86
Methylparaben Sodium	1.8	1.8	1.8	1.8
Glycerin	504	504	504	504
Sodium Hydroxide Solution	QS	QS	QS	QS
Hydrochloric Acid Solution	QS	QS	QS	QS
pH	4	5	6	7
Purified Water QS to	1 mL	1 mL	1 mL	1 mL
Purified Water QS to	1 mL	1 mL	1 mL	1 mL

The liothyroinie liquid oral dosage forms described in Table 2 were packed in various configurations including amber glass bottles, amber PET bottles, clear glass bottles and white HDPE bottles. The bottles were sealed and stored at 5°C, 25°C, and 40°C for at least 3 months or longer. A summary of the stability results for lots PD-0021-019 and PD-0021-22 are as follows:

5

PD-0021-109 60 mL fill in 2 oz. bottles							
Condition (°C)	**Packaging Container**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial							
40	Clear Glass	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
25	Clear Glass	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
5	Clear Glass	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
40	Amber Glass	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
25	Amber Glass	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
5	Amber Glass	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
40	Amber PET	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
25	Amber PET	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
5	Amber PET	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
40	White HDPE	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
25	White HDPE	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
5	White HDPE	Clear Colorless Solution	4.4	101.6	0.120	0.120	0.429
3 Months							
40	Amber Glass	Clear Colorless Solution	4.1	95.7	0.299	0.394	0.645
40	Clear Glass	Clear Colorless Solution	4.2	92.2	0.232	0.312	0.662
40	Amber PET	Clear Colorless Solution	3.8	96.0	0.420	0.495	0.750
40	White HDPE	Clear Colorless Solution	3.8	94.5	0.421	0.720	0.969

25	Amber Glass	Clear Colorless Solution	4.1	96.7	0.176	0.244	0.558
25	Clear Glass	Clear Colorless Solution	4.1	97.0	0.169	0.234	0.548
25	Amber PET	Clear Colorless Solution	3.9	95.7	0.194	0.263	0.579
25	White HDPE	Clear Colorless Solution	3.9	95.4	0.186	0.250	0.563
5	Amber Glass	Clear Colorless Solution	4.1	96.7	0.065	0.065	0.373
5	Clear Glass	Clear Colorless Solution	4.1	96.0	0.068	0.068	0.373
5	Amber PET	Clear Colorless Solution	4.0	95.2	0.064	0.064	0.376
5	White HDPE	Clear Colorless Solution	3.9	95.5	0.062	0.062	0.374
6 Months							
5	Amber Glass	Clear Colorless Solution	4.0	95.3	0.10	0.15	0.48
5	Amber PET	Clear Colorless Solution	4.0	95.3	0.15	0.28	0.62
25	Amber Glass	Clear Colorless Solution	4.0	95.7	0.18	0.31	0.65
25	Amber PET	Clear Colorless Solution	3.9	97.3	0.25	0.38	0.74
40	Amber Glass	Clear Colorless Solution	4.1	94.4	0.28	0.93	1.26
40	Amber PET	Clear Colorless Solution	3.8	94.7	0.31	1.07	1.39

RS = related substances, i.e. degradation products and impurities

PD-0021-022 60 mL fill in 2 oz. bottles							
Condition (°C)	**Packaging Container**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial							
40	Clear Glass	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
25	Clear Glass	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
5	Clear Glass	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309

40	Amber Glass	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
25	Amber Glass	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
5	Amber Glass	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
40	Amber PET	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
25	Amber PET	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
5	Amber PET	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
40	White HDPE	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
25	White HDPE	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
5	White HDPE	Clear Colorless Solution	5.0	99.6	0.000	0.000	0.309
3 Months							
40	Amber Glass	Clear Colorless Solution	5.0	94.7	0.057	0.057	0.330
40	Clear Glass	Clear Colorless Solution	5.0	94.5	0.158	0.306	0.679
40	Amber PET	Clear Colorless Solution	4.7	94.4	0.088	0.176	0.434
40	White HDPE	Clear Colorless Solution	4.6	94.0	0.127	0.312	0.565
25	Amber Glass	Clear Colorless Solution	5.0	96.6	0.072	0.072	0.387
25	Clear Glass	Clear Colorless Solution	5.0	96.3	0.069	0.069	0.381
25	Amber PET	Clear Colorless Solution	4.9	95.8	0.068	0.068	0.380

25	White HDPE	Slight cloudy colorless solution with floating particles	4.8	95.4	0.070	0.070	0.387
5	Amber Glass	Clear Colorless Solution	5.1	95.9	0.069	0.069	0.379
5	Clear Glass	Clear Colorless Solution	5.1	95.9	0.063	0.063	0.368
5	Amber PET	Clear Colorless Solution	5.0	95.3	0.065	0.065	0.371
5	White HDPE	Clear Colorless Solution	4.9	95.6	0.063	0.063	0.374
6 Months							
5	Amber Glass	Clear Colorless Solution	5.0	95.3	0.12	0.30	0.63
5	Amber PET	Clear Colorless Solution	4.9	95.1	0.12	0.18	0.53
25	Amber Glass	Clear Colorless Solution	5.0	95.3	0.08	0.20	0.56
25	Amber PET	Clear Colorless Solution	4.8	96.1	0.06	0.22	0.57
40	Amber Glass	Clear Colorless Solution	4.9	94.4	0.20	0.73	1.12
40	Amber PET	Clear Colorless Solution	4.6	93.9	0.13	0.54	0.88

Stability testing for Lots PD-0021-025 and PD-0021-028 were discontinued shortly after preparation due to the high amount of impurities and/or degradation products.

The above data shows that after three months the liothyronine liquid dosage forms with a pH of less than 6 maintained 90%-110% of the original amount of liothyronine; maintained a pH of ± 0.5 of the target pH; contained less than 0.75% of any individual liothyronine degradation product or impurity and contained less than 2.0% of a combined total amount of liothyronine degradation products and/or impurities when stored in amber glass bottles or amber PET bottles.

Table 3 Composition of Liothyronine Sodium Oral Solution

Ingredients	Lot: PD-0021-031 mg/mL	Lot: PD-0021-034 mg/mL	Lot: PD-0021-037 mg/mL	Lot: PD-0021-040 mg/mL	Lot: PD-0021-043 mg/mL	Lot: PD-0021-046 mg/mL	Lot: PD-0021-049 mg/mL
Liothyronine sodium*	0.005169	0.005169	0.005169	0.005169	0.005169	0.005169	0.005169
Citric acid Anhydrous	1.44	1.44	1.44	1.44	1.44	1.44	1.44
Sodium Citrate Dihydrate	3.68	3.68	3.68	3.68	3.68	3.68	3.68
Methylparaben Sodium	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Glycerin	-	-	-	252	756	504	504
Sodium Hydroxide Solution	QS	QS	QS	QS	QS	QS	QS
Hydrochloric Acid Solution	QS	QS	QS	QS	QS	QS	QS
Hydroxypropyl Beta Cyclodextrin	50	100	150	-	-	-	-
Ethyl alcohol 190 Proof	-	-	-	-		50	50
Potassium Hydroxide	-	-	-	-	-		QS
pH	5	5	5	5	5	5	5
Purified Water QS to	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL

Stability testing for Lots PD-0021-040 and PD-0021-046 were discontinued shortly after preparation due to the high amount of impurities and/or degradation products.

Lots PD-0021-034 and PD0021-037 were packed in various configurations including amber glass bottles, amber PET bottles, clear glass bottles and white HDPE bottles and exhibit greater than 2.5% of any individual liothyronine degradation product upon initial testing.

Lots PD-0021-031 was packed in various configurations including amber glass bottles, amber PET bottles, clear glass bottles and white HDPE bottles. The bottles were sealed and stored at 5°C, 25°C, and 40°C for at least 3 months. Lot PD-0021-031 had high variability with the assay of liothyronine, methylparaben sodium and p-benzoic acid and therefore was determined not to be suitable for future development.

The stability results for Lot PD-0021-0043 in 60 mL fill in 2 oz. bottles was determined as follows:

Condition (°C)	Packaging Container	Appearance	pH	Assay (%)	Highest Unidentified (%)	Total Unidentified (%)	Total RS(%)
Initial							
40	Clear Glass	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
25	Clear Glass	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
5	Clear Glass	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
40	Amber Glass	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
25	Amber Glass	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
5	Amber Glass	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
40	Amber PET	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
25	Amber PET	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
5	Amber PET	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
40	White HDPE	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
25	White HDPE	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
5	White HDPE	Clear Colorless Solution	5.0	94.2	0.000	0.000	0.291
3 Months							
40	Amber Glass	Clear Colorless Solution	5.1	91.8	0.248	0.733	1.251

40	Clear Glass	Clear Colorless Solution	5.0	89.9	0.239	0.710	1.180
40	Ambet PET	Clear Colorless Solution	5.1	95.2	0.000	0.000	0.000
40	White HDPE	Clear Colorless Solution	5.1	92.2	0.000	0.000	0.000
25	Amber Glass	Clear Colorless Solution	5.0	93.0	0.000	0.000	0.000
25	Clear Glass	Slight cloudy colorless solution with floating particles	5.1	92.7	0.000	0.000	0.000
25	Ambet PET	Clear Colorless Solution	5.0	92.8	0.000	0.000	0.000
25	White HDPE	Clear Colorless Solution	5.0	92.4	0.000	0.000	0.000
5	Amber Glass	Clear Colorless Solution	5.0	92.8	0.000	0.000	0.000
5	Clear Glass	Clear Colorless Solution	5.0	93.1	0.000	0.000	0.000
5	Ambet PET	Clear Colorless Solution	5.1	92.5	0.000	0.000	0.000
5	White HDPE	Clear Colorless Solution	5.1	92.7	0.000	0.000	0.000
6 Months							
5	Amber Glass	Clear Colorless Solution	5.0	92.6	0.11	0.24	0.63
5	Amber PET	Clear Colorless Solution	5.0	92.4	0.06	0.06	0.45
25	Amber Glass	Clear Colorless Solution	5.0	92.5	0.16	0.28	0.84
25	Amber PET	Clear Colorless Solution	5.0	93.0	0.18	0.32	0.91

40	Amber Glass	Clear Colorless Solution	5.1	88.3	0.63	2.51	3.13
40	Amber PET	Clear Colorless Solution	5.1	88.1	0.61	2.40	3.02

Table 4 Composition of Liothyronine Sodium Oral Solution

Ingredients	Lot: PD-0021-052 mg/mL	Lot: PD-0021-055 mg/mL	Lot: PD-0021-058 mg/mL	Lot: PD-0021-061 mg/mL
Liothyronine sodium*	0.005169	0.005169	0.005169	0.005169
Citric acid Anhydrous	1.44	1.44	1.44	1.44
Sodium Citrate Dihydrate	3.68	3.68	3.68	3.68
Methylparaben Sodium	1.8	1.8	1.8	1.8
Glycerin	252	252	504	
Sodium Hydroxide Solution	QS	QS	QS	QS
Hydrochloric Acid Solution	QS	QS	QS	QS
Edetate Disodium	-	-	0.5	0.5
Hydroxypropyl Beta Cyclodextrin	-	-	-	100
Propylene Glycol	208	-	-	-
PEG 400	-	226	-	-
pH	§	§	§	§
Purified Water QS to	1 mL	1 mL	1 mL	1 mL

The above liothyronine liquid oral dosage forms were packed in various configurations including amber glass bottles, amber PET bottles, clear glass bottles and white HDPE bottles. The bottles were sealed and stored at 5°C, 25°C, and 40°C for at least 3 months. Stability testing for Lot PD-0021-055 was discontinued shortly after preparation due to the high amount of impurities and/or degradation products. Stability testing for Lot PD-0021-052 and Lot PD-0021-061 were terminated because of unacceptable high assay variations. The stability results for Lot PD-0021-058, 60 mL fill in 2 oz. bottles are shown below:

Condition (°C)	Packaging Container	Appearance	pH	Assay (%)	Highest Unidentified (%)	Total Unidentified (%)	Total RS(%)
Initial							
40	Clear Glass	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
25	Clear Glass	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
5	Clear Glass	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
40	Amber Glass	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
25	Amber Glass	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
5	Amber Glass	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
40	Amber PET	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
25	Amber PET	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
5	Amber PET	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
50	White HDPE	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
40	White HDPE	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
25	White HDPE	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
5	White HDPE	Clear Colorless Solution	5	91.1	0.097	0.097	0.428
3 Months							
40	Amber Glass	Clear Colorless Solution	5.0	87.5	0.251	0.831	1.274

40	Clear Glass	Clear Colorless Solution	5.0	87.1	0.264	1.111	1.523
40	Amber PET	Clear Colorless Solution	5.0	94.1			
40	White HDPE	Clear Colorless Solution	5.0	87.9			
25	Amber Glass	Clear Colorless Solution	5.0	87.4			
25	Clear Glass	Clear Colorless Solution	5.0	92.1			
25	Amber PET	Clear Colorless Solution	5.0	93.9			
25	White HDPE	Clear Colorless Solution	5.0	88.3			
5	Amber Glass	Clear Colorless Solution	5.0	87.8			
5	Clear Glass	Clear colorless solution with tiny particles setting down	5.0	88.1			
5	Amber PET	Clear Colorless Solution	2.0	93.4			
5	White HDPE	Clear Colorless Solution	5.0	88.0			

EXAMPLE 2

Further experiments were conducted to evaluated additional buffer types such as acetate buffer, malate buffer, and tartrate buffer at pH 4.0 and 5.0 with 40% v/v glycerin. The compositions of these liothyronine liquid oral dosage forms are shown below in Table 5.

Table 5 Composition of Liothyronine Sodium Oral Solution

	Lot: PD-0021-084	Lot: PD-0021-086	Lot: PD-0021-088	Lot: PD-0021-090	Lot: PD-0021-092	Lot: PD-0021-094
	mg/mL	mg/mL	mg/mL	mg/mL	mg/mL	mg/mL
Liothyronine Sodium	0.005169	0.005169	0.005169	0.005169	0.005169	0.005169
Acetic Acid Glacial	1.02	0.4019	-	-	-	-
Sodium Acetate Trihydrate	0.4135	1.81	-	-	-	-
DL Malic Acid	-	-	2.68	2.68	-	-
Sodium Hydroxide	-	-	0.72	1.26	-	-
L(+)-Tartaric acid ≥99.5%, granular	-	-	-	-	3	3
Sodium Hydroxide	-	-	-	-	1.08	1.51
Methylparaben Sodium	1.8	1.8	1.8	1.8	1.8	1.8
Glycerin	504	504	504	504	504	504
Sodium Hydroxide Solution	QS	QS	QS	QS	QS	QS
Hydrochloric Acid Solution	QS	QS	QS	QS	QS	QS
pH	4.0	5.0	4.0	5.0	4.0	5.0
Purified Water QS to	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL

The above compositions were packed in amber glass bottles and amber PET bottles. The bottles were sealed and stored at 5°C, 25°C, and 40°C for at least 3 months. These compositions failed to meet the stability criteria because of high assay variability and/or unacceptable levels of liothyronine degradation products and impurities.

The stability data for these alternate buffers demonstrated superior stability of liothyronine liquid oral dosage forms comprising citrate buffer, preferably sodium citrate/citric acid buffer system, and phosphate buffer system, at pH 4.0-5.0 as compared to the alternate buffers evaluated in this Example.

EXAMPLE 3

Table 6 provides the compositions of liothyronine liquid oral dosage forms prepared in accordance with the present invention and prepared at pH 4.5 for with citrate buffers or phosphate buffers and with 40% v/v glycerin.

Table 6 Composition of Liothyronine Sodium Oral Solution

	Lot: PD-0021-100*	**Lot: PD-0021-102***	**Lot: PD-0021-108**
	mg/mL	**mg/mL**	**mg/mL**
Liothyronine Sodium	0.005169	0.005169	0.005169
Citric Acid Anhydrous	1.93	-	1.93
Sodium Citrate Dihydrate	2.93	-	2.93
Monobasic Sodium Phosphate Monohydrate	-	2.74	-
Dibasic Sodium Phosphate Heptahydrate	-	0.04	-
Methylparaben Sodium	1.8	1.8	1.8
Glycerin	504*	504*	504
Sodium Hydroxide Solution	QS	QS	QS
Hydrochloric Acid Solution	QS	QS	QS
pH	4.5	4.5	4.5
Purified Water QS to	1 mL	1 mL	1 mL

Table 7 (continued)

	Lot: PD-0021-110	**Lot: PD-0021-112**	**Lot: PD-0021-137**
	mg/mL	**mg/mL**	**mg/mL**
Liothyronine Sodium	0.005169	0.005169	0.005169
Citric Acid Anhydrous	-	2.41	-
Sodium Citrate Dihydrate	-	2.2	-
Monobasic Sodium Phosphate Monohydrate	2.74	-	2.74
Dibasic Sodium Phosphate Heptahydrate	0.04	-	0.04
Methylparaben Sodium	1.8	1.8	1.8**
Glycerin	504	504	504
Sodium Hydroxide Solution	QS	QS	QS
Hydrochloric Acid Solution	QS	QS	QS
pH	4.5	4.0	4.5
Purified Water QS to	1 mL	1 mL	1 mL

*Synthetic Glycerin

**material obtained from an alternate source

The above compositions were prepared by the following process:

(i) adding and mixing about 20 wt% of the final amount of purified water, buffer agent and cosolvent to a batch tank;

(ii) using a sample of the step (i) solution to wet the liothyronine in an appropriate container;

(iii) adding the with wet liothyronine to the batch tank of step (i) and mix until liothyronine is dissolved;

(iv) after the liothyronine is dissolved adding water to the batch tank of step (iii) to obtain about 90% of batch size and then adding preservatives/antimicrobial agents and mixing to obtain a prefinal solution;

(v) measuring and adjusting the pH of the prefinal solution of step (iv) to a target pH of preferably about 4 to about 5;

(vi) adding purified water to the solution of step (v) to obtain the desired concentration/volume;

(vii) filtering and packaging the final liothyronine solution of step (vi).

The liquid oral dosage forms may be packaged in amber glass bottles such as 40-240 mL amber glass bottles or amber PET bottles such as 40-480 mL amber PET bottles with appropriate closures. Representative examples include but are not limited to:

Packaging Type A

- 120 mL in Amber Glass
- Bottle: 125 mL Amber Glass Bottle by Stoelzle Oberglas Gmbh, Berlin Part: 72434
- Caps: SENSOkidCap PP28 T/E by Sensoplast, Berlin Part:89190040879

Packaging Type B1

- 40 mL in Amber PET
- Bottle: 45 mL Amber PET bottle BR/Ss 20-B LAM 640/CS
- Caps: PDT20 WHT/(F39)FS3-19/C25.035 PLN foam

Packaging Type B2

- 150 mL in Amber PET
- Bottle: B150 mL BR/AV 24-B DAM 440/CS VR3320
- Caps: CLS-24/400 White CRC ASHL/PET .035 C25 FSLE 3-19 Liner VR3321

Packaging Type B3

- 480 mL in Amber PET
- Bottle: 16 oz Boston Round PET, 24-400 CT VR3230
- Caps: 24 mm CRC PDT24 CQA-10155 VR3225

The stability testing for lots PD-0021-100, PD-0021-102 were discontinued because of high assay variability and/or unacceptable levels of liothyronine degradation products and impurities. The stability testing for Lot PD0021-137 was discontinued for administrative reasons.

The stability for the remaining lots are as follows:

PD-0021-108 60 mL fill in 2 oz. Bottles							
Condition (°C)	**Packaging Container**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial							
Initial	Amber Glass	Clear colorless solution with floating particles	4.5	89.3	0.33	0.55	0.94
1 Month							
40C	Amber Glass	Clear colorless solution	4.5	87.0	0.28	0.60	0.99
40C	Amber PET	Clear colorless solution	4.5	86.6	0.29	1.03	1.45
3 Months							
5C	Amber Glass	Clear colorless solution	4.6	89.5	0.44	0.52	0.96
5C	Amber PET	Clear colorless solution	4.6	89.3	0.43	0.50	0.92
25C	Amber Glass	Clear colorless solution	4.6	88.9	0.43	0.57	0.99
25C	Amber PET	Clear colorless solution	4.6	89.0	0.42	0.75	1.20

40C	Amber Glass	Clear colorless solution	4.7	84.9	0.41	2.22	2.65
40C	Amber PET	Clear colorless solution	4.7	84.4	0.43	2.15	2.59
6 Months							
5C	Amber Glass	Clear colorless solution	4.3	88.2	0.40	0.40	0.78
5C	Amber PET	Clear colorless solution	4.3	88.6	0.40	0.40	0.77
25C	Amber Glass	Clear colorless solution	4.3	87.3	0.39	0.66	1.05
25C	Amber PET	Clear colorless solution	4.3	87.7	0.39	0.93	1.32
40C	Amber Glass	Clear colorless solution	4.4	80.1	0.81	2.60	2.94
40C	Amber PET	Clear colorless solution	4.4	79.3	0.77	2.69	2.97

PD-0021-110 (60 mL Fill in 2 oz. Bottles							
Condition (°C)	**Packaging Container**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial							
Initial	Amber Glass	Clear colorless solution	4.7	88.3	0.34	0.45	0.84
1 Month							
40C	Amber Glass	Clear colorless solution	4.7	86.6	0.28	0.49	0.86
40C	Amber PET	Clear colorless solution	4.4	87.6	0.32	0.56	0.93
3 Months							
5C	Amber Glass	Clear colorless solution	4.7	88.5	0.44	0.51	0.93

5C	Amber PET	Clear colorless solution	4.6	94.6	0.44	0.51	0.95
25C	Amber Glass	Clear colorless solution	4.7	88.6	0.43	0.52	0.94
25C	Amber PET	Clear colorless solution	4.5	90.8	0.44	0.59	1.01
40C	Amber Glass	Clear colorless solution	4.8	87.4	0.46	0.63	1.01
40C	Amber PET	Clear colorless solution	4.5	88.1	0.44	0.64	1.05
6 Months							
5C	Amber Glass	Clear colorless solution	4.3	88.0	0.40	0.40	0.76
5C	Amber PET	Clear colorless solution	4.2	91.1	0.41	0.41	0.80
25C	Amber Glass	Clear colorless solution	4.3	87.7	0.42	0.50	0.88
25C	Amber PET	Clear colorless solution	4.1	92.9	0.42	0.57	0.95
40C	Amber Glass	Clear colorless solution	4.5	86.5	0.45	0.45	0.81
40C	Amber PET	Clear colorless solution	4.1	88.8	0.41	0.55	0.90

PD-0021-112 60 mL fill in 2 oz. bottles							
Condition (°C)	**Packaging Container**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial	Amber Glass	Clear colorless solution	4.0	93.6	0.56	0.72	1.15
1 Month							

40C	Amber Glass	Clear colorless solution	4.0	90.1	0.49	0.84	1.27
40C	Amber PET	Clear colorless solution	4.0	89.6	0.50	1.14	1.59
3 Months							
5C	Amber Glass	Clear colorless solution	4.1	95.1	0.64	0.80	1.26
5C	Amber PET	Clear colorless solution	4.1	91.6	0.65	0.71	1.17
25C	Amber Glass	Clear colorless solution	4.1	92.8	0.64	0.87	1.35
25C	Amber PET	Clear colorless solution	4.1	90.9	0.63	0.93	1.42
40C	Amber Glass	Clear colorless solution	4.2	92.5	0.59	2.61	3.02
40C	Amber PET	Clear colorless solution	4.1	86.2	0.64	2.21	2.68
6 Months							
5C	Amber Glass	Clear colorless solution	3.7	94.1	0.65	0.82	1.22
5C	Amber PET	Clear colorless solution	3.7	90.7	0.62	0.78	1.19
25C	Amber Glass	Clear colorless solution	3.8	90.6	0.62	1.41	1.80
25C	Amber PET	Clear colorless solution	3.7	90.1	0.63	1.39	1.74
40C	Amber Glass	Clear colorless solution	3.8	78.9	0.89	3.36	3.62
40C	Amber PET	Clear colorless solution	3.8	82.7	0.60	2.83	3.12

The foregoing stability data for the dosage forms with a pH of 4.5 citrate buffer, 40% v/v glycerin and either a citrate or phosphate buffer is comparable to the previous data provided in Examples 1 and 2 at pH 4.0 and pH 5.0 for these buffers.

EXAMPLE 4

The following composition was prepared on a commercial scale (1000L) according to the procedure outlined in Example 3

	mg/mL
Liothyronine Sodium	0.005169
Monobasic Sodium Phosphate Monohydrate	2.74
Dibasic Sodium Phosphate Heptahydrate	0.04
Methylparaben Sodium	1.8
Glycerin	504
Sodium Hydroxide Solution	QS
Hydrochloric Acid Solution	QS
pH	4.5
Purified Water QS to	1 mL

The liquid oral dosage forms may be packaged in amber glass bottles such as 40-240 mL amber glass bottles or amber PET bottles such as 40-480 mL amber PET bottles with appropriate closures as described in Example 3 or the following:

Packaging Type C1

- 120 mL in Amber Glass
- Bottle: 125 mL Amber Glass Bottle by Stoelzle Oberglas Gmbh, Berlin Part: 72434
- Caps: SENSOkidCap PP28 T/E by Sensoplast, Berlin Part:89190040879

Packaging Type C2

- 40 mL in Amber PET
- Bottle: 45 mL Amber PET bottle BR/Ss 20-B LAM 640/CS
- Caps: PDT20 WHT/(F39)FS3-19/C25.035 PLN foam

Packaging Type C3

- 150 mL of the liquid liothyronine in an Amber PET
- Bottle: 150 mL Boston Round Dark Amber PET 24/410
- Caps: CLS-24/400 White CRC ASHL/PET .035 C25 FSLE 3-19 Liner VR3321

Packaging Type C4

- 480 mL of liquid liothyronine in an Amber PET

- Bottle: 16 oz Boston Round PET, 24-400 CT
- Caps: 24 mm CRC PDT24 CQA-10155 VR3225

The commercial scale lots of the liothyronine liquid oral dosage forms described in Example 4 were packaged and placed on stability. The following results were obtained.

150 mL/Amber PET Bottle (Lot RB01435044)							
Condition (°C)	**Orientation**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial		Clear colorless solution	4.4	92.0	0.21	0.38	0.80
1 Month							
25C	Up	Clear colorless solution	4.3	90.6	0.21	0.56	1.01
25C	Inv	Clear colorless solution	4.3	90.6	0.20	0.59	1.02
40C	Up	Clear colorless solution	4.2	90.3	0.20	0.46	0.90
40C	Inv	Clear colorless solution	4.2	90.4	0.21	0.65	1.09
3 Months							
25C	Inv	Clear colorless solution	3.9	91.6	0.21	0.44	0.82
40C	Inv	Clear colorless solution	3.9	91.3	0.22	0.56	0.96
6 Months							
25C	Up	Clear colorless solution	4.2	90.3	0.22	0.52	0.90
25C	Inv	Clear colorless solution	4.2	90.4	0.23	0.58	0.94

40C	Up	Clear colorless solution	4.1	89.5	0.24	0.70	1.08
40C	Inv	Clear colorless solution	4.1	89.5	0.25	0.82	1.19

Up = bottle in normal position with the liquid not in contact with the cap

Inv = inverted with liquid in contact with the cap.

120 mL Amber Glass Bottle (RB01435045)							
Condition (°C)	**Orientation**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial		Clear colorless solution	4.4	91.9	0.20	0.35	0.78
25C	Up	Clear colorless solution	4.3	90.5	0.19	0.51	0.94
25C	Inv	Clear colorless solution	4.3	90.7	0.10	0.25	0.70
40C	Up	Clear colorless solution	4.3	90.4	0.17	0.39	0.83
40C	Inv	Clear colorless solution	4.3	90.3	0.22	0.50	0.93
25C	Inv	Clear colorless solution	4.0	91.8	0.20	0.35	0.76
40C	Inv	Clear colorless solution	4.0	91.2	0.19	0.35	0.74
25C	Up	Clear colorless solution	4.2	90.4	0.20	0.26	0.63
25C	Inv	Clear colorless solution	4.2	90.0	0.21	0.27	0.64

40C	Up	Clear colorless solution	4.2	89.0	0.20	0.45	0.83
40C	Inv	Clear colorless solution	4.2	88.8	0.19	0.48	0.84

480 mL Amber PET Bottle (RB01435042)							
Condition (°C)	**Orientation**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial		Clear colorless solution	4.4	91.7	0.20	0.36	0.78
1 Month							
25C	Up	Clear colorless solution	4.3	90.2	0.19	0.34	0.81
25C	Inv	Clear colorless solution	4.2	90.5	0.18	0.35	0.81
40C	Up	Clear colorless solution	4.2	90.2	0.20	0.46	0.89
40C	Inv	Clear colorless solution	4.2	90.2	0.21	0.64	1.08
3 Months							
25C	Inv	Clear colorless solution	3.9	91.7	0.21	0.37	0.77
40C	Inv	Clear colorless solution	3.9	91.7	0.20	0.39	0.76
6 Months							
25C	Up	Clear colorless solution	4.2	90.4	0.22	0.38	0.78
25C	Inv	Clear colorless solution	4.2	90.5	0.22	0.37	0.73
40C	Up	Clear colorless solution	4.1	89.2	0.23	0.68	1.06

40C	Inv	Clear colorless solution	4.1	89.1	0.23	0.67	1.04

EXAMPLE 5

The following composition was prepared

	mg/mL
Liothyronine Sodium	0.005169
Monobasic Sodium Phosphate Monohydrate	2.74
Dibasic Sodium Phosphate Heptahydrate	0.04
Methylparaben Sodium	1.8
Glycerin	504
Sodium Hydroxide Solution	QS
Hydrochloric Acid Solution	QS
pH	4.5
Purified Water QS to	1 mL

The above composition was prepared by the following process:

(i) adding and mixing about 35-60 wt%, preferably about 40-55 wt% and more preferably 45-50 wt% of the final amount of purified water to a batch tank;

(ii) adding the dibasic sodium phosphate to the water in the batch tank of step (i) and mixing for not less than 5 minutes or until the dibasic sodium phosphate is dissolved;

(iii) adding the monobasic sodium phosphate to the solution of step (ii) and mixing for not less than 5 minutes or until the monobasic sodium phosphate is dissolved;

(iv) adding glycerin to the solution of step (iii) and mixing for not less than 5 minutes or until a uniform composition is obtained;

(v) add about 2-15%, preferably about 2-10% and more preferably about 3-7% of the batch weight of purified water to a separate side tank.

(vi) add the methylparaben sodium to purified water in the side tank of step (v);

(vii) removing a sample of the solution prepared in step (vi)

(viii) wetting the liothyronine in an appropriate container with a portion of the sample solution from step (vii);

(ix) adding the wet liothyronine of step (vii) to the solution in the separate side tank of step (vi) and mixing until liothyronine is dissolved;

(x) rinsing the container which held the wet liothyronine, preferably 1, 2, 3 or more times, with the remaining sample solution of step (vii) or portions therefore and adding the rinse liquid into the solution in the side tank of step (ix);

(xi) adding any remaining amounts of the sample from step (vii) to the solution prepared in step (ix);

(xii) adding the solution of step (x) or (xi) to the solution of step (iv);

(xiii) measuring and adjusting the pH of the prefinal solution of step (xii) to a target pH of preferably about 4.5 to about 5.5, preferably about 5.0 with HCl and/or NaOH;

(xiv) adding purified water to the solution of step (xiii) to obtain the desired concentration/volume;

(xv) filtering and packaging the final liothyronine solution of step (xiv).

The composition was packaged in amber glass and amber PET bottles and the stability was tested. The following results were obtained:

PD-0021-144 60 mL fill in 2 oz. Bottles							
Condition (°C)	**Packaging Container**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial	Amber Glass	Clear colorless solution	4.7	98.2	0.09	0.15	0.69
18 Hrs./RT	Amber Glass	Clear colorless solution	4.6	99.7	0.10	0.10	0.65
1 Month							
40C	Amber Glass	Clear colorless solution	4.7	98.6	0.10	0.10	0.58
25C	Amber Glass	Clear colorless solution	4.6	98.8	0.08	0.08	0.58
40C	Amber PET	Clear colorless solution	4.4	98.6	0.11	0.21	0.69
25C	Amber PET	Clear colorless solution	4.5	98.9	0.00	0.00	0.48
3 Months							

40C	Amber Glass	Clear colorless solution	4.5	98.1	0.13	0.13	0.65
25C	Amber Glass	Clear colorless solution	4.4	98.9	0.14	0.22	0.71
40C	Amber PET	Clear colorless solution	4.1	98.6	0.22	0.81	1.32
25C	Amber PET	Clear colorless solution	4.2	99.0	0.08	0.15	0.65

It was determined that the above process which added the antimicrobial/preservative, methylparaben sodium, to the solution used to wet the liothyronine and prior to adding the liothyronine to the batch tank as described in Example 3, improved the assay values for liothyronine liquid oral dosage form, i.e. final composition.

A commercial scale lot of the liothyronine liquid oral dosage form described in Example 5 was packaged and placed on stability. The following results were obtained:

150 ml Amber PET Bottles (RB01435050)							
Condition (°C)	**Orientation**	**Appearance**	**pH**	**Assay (%)**	**Highest Unidentified (%)**	**Total Unidentified (%)**	**Total RS(%)**
Initial		Clear colorless solution	4.6	97.7	0.00	0.00	0.49
1 Month							
40C	Inv	Clear colorless solution	4.2	96.0	0.26	0.46	0.88
40C	UP	Clear colorless solution	4.2	96.0	0.27	0.46	0.92
3 Months							
25C	Inv	Clear colorless solution	4.3	94.1	0.17	0.54	0.94
40C	Inv	Clear colorless solution	4.2	94.5	0.17	0.46	0.85

The invention described herein may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example,

in each instance herein, any of the terms "comprising," "consisting essentially of," and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the claims.

CLAIMS

1. A liquid oral liothyronine dosage form comprising:

(a) 0.1 µg/mL to about 200 µg/mL liothyronine or a pharmaceutically acceptable salt thereof;

(b) water;

(c) at least one buffering agent, selected from a citrate buffer, a phosphate buffer or combination thereof to maintain the pH of the liquid oral dosage form within the target pH of 3.5 to 5.5 during storage; and

(d) a solvent

wherein when the liquid dosage form is packed in an amber glass bottle or amber polyethylene terephthalate bottle with the plastic cap and stored for three months at 25°C and 60% relative humidity, the liquid dosage form comprises: (i) 90%-110% of the labeled amount of liothyronine; (ii) about 1.0% or less of any individual liothyronine degradation product or impurity; (iii) a total amount of liothyronine degradation products and/or impurities of about 2.0% or less and (iv) the pH is ± 0.75 of the initial pH.

2. The liquid dosage form of claim 1 further comprising one or more antimicrobial agents, preservatives, pH adjusting agents; flavoring agents, chelating agents, viscosity enhancing agents, solubility enhancing agents, coloring agents or combinations thereof.

3. The liquid dosage form of claim 1 wherein when the liquid dosage form is packed in an amber glass bottle or amber polyethylene terephthalate bottle with the plastic cap and stored for six months at 25°C and 60% relative humidity, the liquid dosage form comprises: (i) 90%-110% of the labeled amount of liothyronine; (ii) about 1.0% or less of any individual liothyronine degradation product or impurity; (iii) a total amount of liothyronine degradation products and/or impurities of about 2.0% or less and (iv) pH is ± 0.75 of the initial pH.

4. The liquid dosage form of claim 1 wherein when the liquid dosage form is packed in an amber glass bottle or amber polyethylene terephthalate bottle with the plastic cap and stored for one month at 40°C and 75% relative humidity, the liquid dosage form comprises: (i) 90%-110% of the labeled amount of liothyronine; (ii) about 1.0% or less of any individual liothyronine

degradation product or impurity; (iii) a total amount of liothyronine degradation products and/or impurities of about 2.0% or less and (iv) pH is ± 0.75 of the initial pH.

5. The liquid dosage form of claim 1 wherein when the liquid dosage form is packed in an amber glass bottle or amber polyethylene terephthalate bottle with the plastic cap and stored for three months at 40°C and 75% relative humidity, the liquid dosage form comprises: (i) 90%-110% of the labeled amount of liothyronine; (ii) about 1.0% or less of any individual liothyronine degradation product or impurity; (iii) a total amount of liothyronine degradation products and/or impurities of about 2.0% or less and (iv) pH is ± 0.75 of the initial pH.

6. The liquid dosage form of claim 1 wherein the solvent is glycerin.

7. The liquid dosage form of claim 7 wherein the dosage form is free of mono-alcohols.

8. The liquid dosage form of claim 1 further comprising an antimicrobial agent or a preservative.

9. The liquid dosage form of claim 8 wherein the antimicrobial agent or preservative is selected from the groups consisting of benzyl alcohol, methylparaben, propylparaben, butylparaben, sorbic acid, benzoic acid, alkali salts of the foregoing and combinations of the foregoing.

10. The liquid dosage form of claim 1 comprising:

(a) liothyronine sodium in an amount to obtain a concentration of about 0.1 µg/mL to about 200 µg/mL liothyronine;

(b) water;

(c) a phosphate buffer in an amount sufficient to maintain the pH of the liquid oral dosage form within the target pH of 3.5 to 5.5 during storage;

(d) glycerin;

(e) an antimicrobial agent or preservative selected from the groups consisting of benzyl alcohol, methylparaben, propylparaben, butylparaben, sorbic acid, benzoic acid, alkali salts of the foregoing and combinations of the foregoing; and

(f) optionally, a pH adjusting agent.

11. The liquid dosage form of claim 10 wherein the antimicrobial agent or preservative is methylparaben, propylparaben, butylparaben or alkali salts thereof.

12. A method for preparing the liquid dosage form of claim 1 comprising:

(i) preparing a first solution comprising water, the buffer, the solvent, and optionally other pharmaceutically acceptable excipients selected from the group consisting of antimicrobial agents, preservatives, flavoring agents, chelating agents, viscosity enhancing agents, solubility enhancing agents, coloring agents or combinations thereof, wherein the first solution is about 1% to about 30% of a final manufacturing batch volume and wherein the first solution has a pH between 3.5 to about 6.5.

(ii) adding a desired amount of the liothyronine or pharmaceutically acceptable salt thereof to the first solution and mixing to obtain a liothyronine concentrate premix solution;

(iii) adding the liothyronine concentrate premix solution to a second solution having the same composition as the first solution only the second solution has a larger volume than the first solution and mixing the liothyronine concentrate premix solution and the second solution to obtain a liothyronine third solution;

(iv) optionally adding water to the liothyronine third solution to obtain a final manufacturing batch volume if necessary so that the final manufacturing batch volume comprise about 0.1 µg/mL to about 200 µg/mL of liothyronine or a pharmaceutically acceptable salt;

(v) packaging the liothyronine liquid dosage form prepared in steps (iii) or (iv) into single or multiple dose containers for distribution to hospitals, pharmacies and/or patients.

13. A method for preparing the liquid oral dosage form of claim 1 comprising:

(ai) preparing a first solution comprising water, the solvent, and the buffer in a first container;

(aii) placing a portion of the first solution in a second container, wherein the portion comprises about 1% to about 50% of the weight or volume of the total weight or volume of the first solution forming a second solution;

(aiii) combining the liothyronine or pharmaceutically acceptable salt thereof and the second solution to form a third solution;

(aiv) adding the third solution to the first solution and mixing to obtain a fourth solution;

(av) optionally adding water to the fourth solution to obtain a final manufacturing batch volume, if necessary, wherein the final manufacturing batch volume comprise about 0.1 µg/mL to about 200 µg/mL of liothyronine or a pharmaceutically acceptable salt;

(avi) packaging the liothyronine liquid dosage form prepared in steps (aiv) or (av) into single or multiple dose containers for distribution to hospitals, pharmacies and/or patients.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/024729

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/08(2006.01)i; **A61K 47/12**(2006.01)i; **A61K 47/02**(2006.01)i; **A61K 47/06**(2006.01)i; **A61K 9/00**(2006.01)i; **A61K 31/27**(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 9/08(2006.01); A61J 7/00(2006.01); A61K 31/195(2006.01); A61K 31/197(2006.01); A61K 9/00(2006.01); A61K 9/48(2006.01); A61P 31/16(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: liothyronine, oral, buffer agent, dosage, liquid

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6458842 B1 (DICKINSON, J. et al.) 01 October 2002 (2002-10-01) claims 1-9	1-13
A	US 10695309 B2 (WESTERN NEW ENGLAND UNIVERSITY) 30 June 2020 (2020-06-30) the entire document	1-13
A	CN 103705497 B (WUHAN WEILIDE BIOLOGICAL PHARMACEUTICAL CO., LTD.) 01 April 2015 (2015-04-01) the entire document	1-13
A	US 2004-0152783 A1 (OLON, L. P. et al.) 05 August 2004 (2004-08-05) the entire document	1-13
A	CN 103987358 B (Altergon S.A.) 26 April 2017 (2017-04-26) the entire document	1-13

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 August 2022	**01 August 2022**

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/024729

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