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Jiang et al.

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(54) **LEVOTHYROXINE FORMULATIONS**

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(51) **Int. Cl.**

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A61K 47/26	(2006.01)
A61K 9/00	(2006.01)
A61K 9/19	(2006.01)

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CPC ***A61K 9/19*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 47/26*** (2013.01); ***A61K 31/198*** (2013.01)

(58) **Field of Classification Search**

CPC ... A61K 31/198; A61K 47/26; A61K 9/0019; A61K 9/19

See application file for complete search history.

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(57) **ABSTRACT**

A levothyroxine composition includes levothyroxine sodium and mannitol. The composition is a solid. The composition may include from 100 to 500 micrograms levothyroxine sodium and from 1 to 5 milligrams mannitol. The composition may include from 100 to 200 micrograms levothyroxine sodium, and the mass ratio of mannitol to levothyroxine sodium in the composition may be at most 40:1. The composition may include about 500 micrograms levothyroxine sodium, and the mass ratio of mannitol to levothyroxine sodium in the composition may be at most 10:1.

21 Claims, 3 Drawing Sheets

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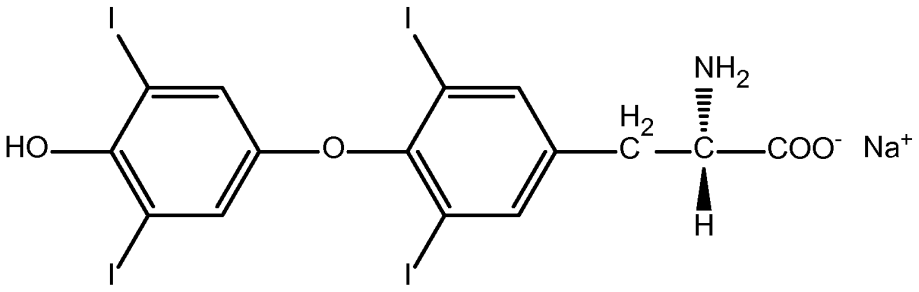

FIG. 1

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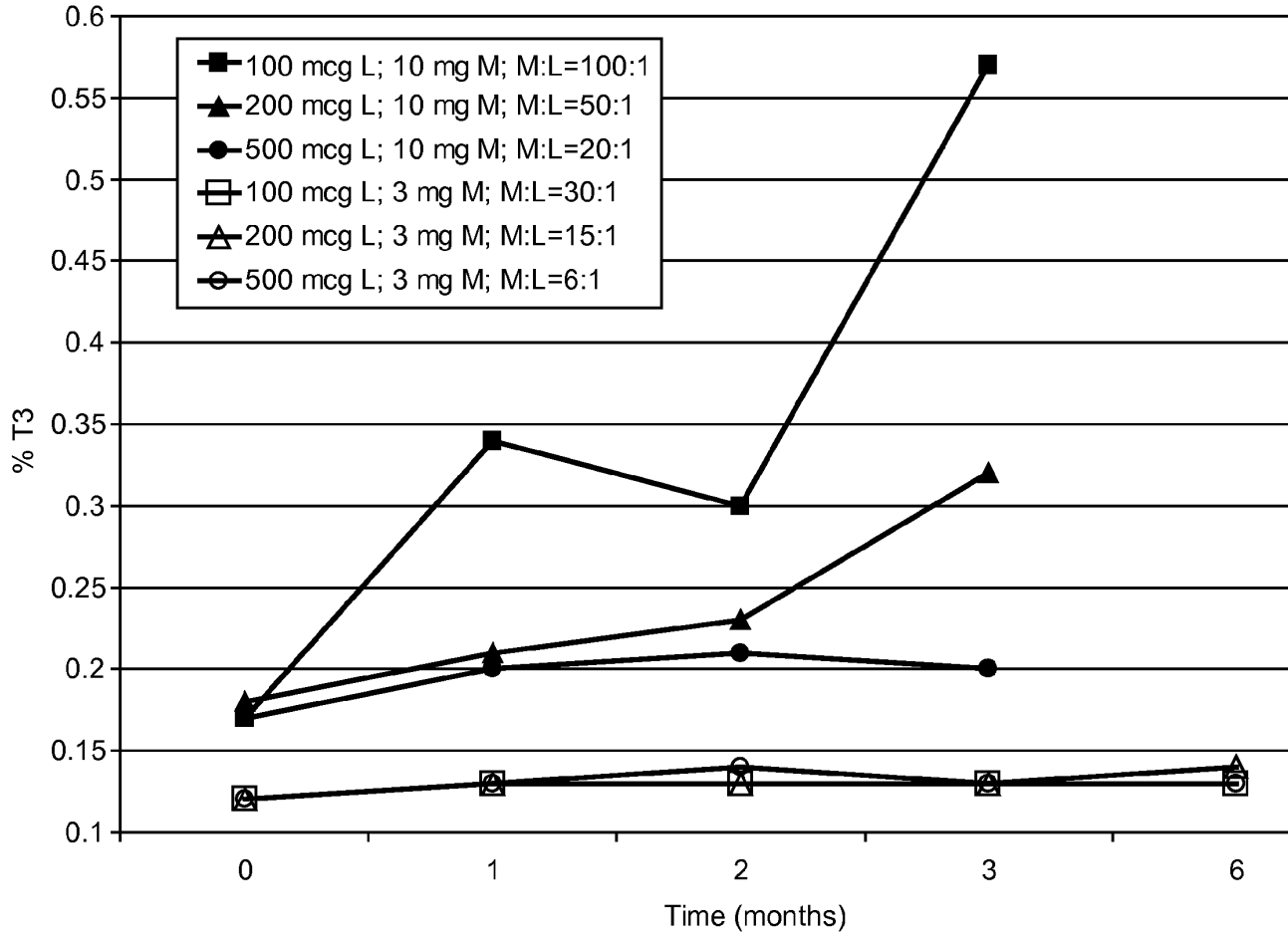

FIG.2

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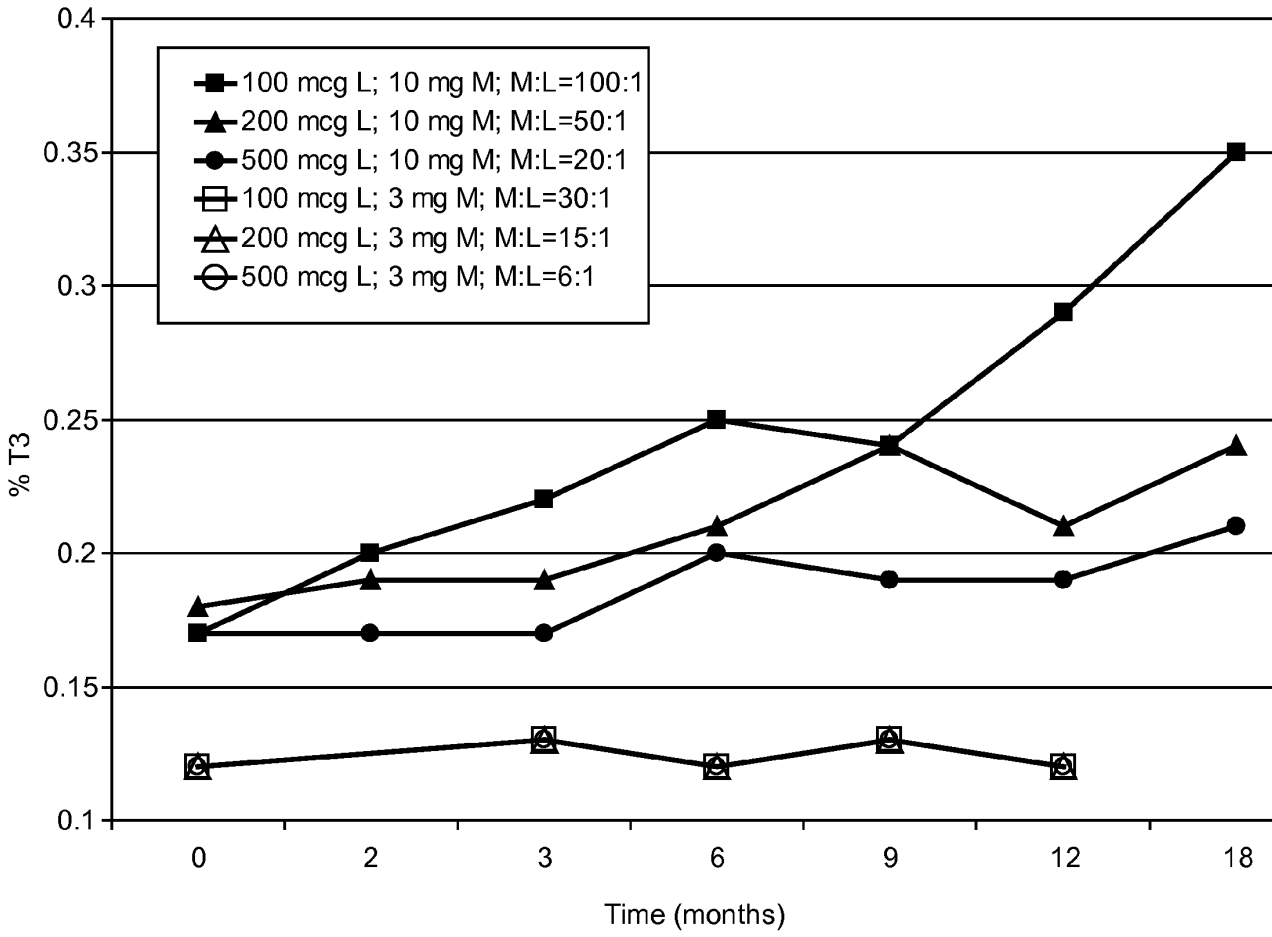

FIG. 3

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LEVOTHYROXINE FORMULATIONS

REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/529,084 entitled "Levothyroxine Formulations" filed Aug. 30, 2011, which is incorporated by reference in its entirety.

BACKGROUND

A healthy thyroid produces hormones that regulate multiple metabolic processes and that play important roles in growth and development, in maturation of the central nervous system and bone including augmentation of cellular respiration and thermogenesis, and in metabolism of proteins, carbohydrates and lipids. The thyroid accomplishes its regulation functions by producing the hormones L-triiodothyronine (liothyronine; T3) and L-thyroxine (levothyroxine; T4).

Thyroid hormones are believed to exert their physiologic actions through control of DNA transcription and protein synthesis. It is presently believed that the T3 and T4 hormones diffuse into the cell nucleus and bind to thyroid receptor proteins attached to DNA. This hormone nuclear receptor complex then activates gene transcription and synthesis of messenger RNA and cytoplasmic proteins. The physiological actions of thyroid hormones are believed to be produced predominantly by T3, approximately 80% of which is derived from T4 by deiodination in peripheral tissues.

Both T3 and T4 are stored in the thyroid as thyroglobulin adducts with serum proteins. Once secreted by the thyroid, T3 and T4 primarily exist in the circulatory system as their thyroglobulin adducts, and are in equilibrium with small amounts (<1%) of the unbound hormones, which are the metabolically active species. T4 has higher serum levels, slower metabolic clearance, and a longer half-life than T3, which may be due to the higher affinity of serum proteins for T4 compared to T3.

A patient who has had their thyroid gland removed, or whose thyroid gland functions at an undesirably low level (hypothyroidism), may be treated by administration of a daily maintenance dose of 50-100 micrograms (μg) of levothyroxine sodium. A patient in need of additional intervention may be treated by administration of an initial dose of 200-500 μg or 300-500 μg of levothyroxine sodium and/or with a 2^{nd} day dose of 100-300 μg of levothyroxine sodium. Formal names for levothyroxine sodium include 4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodo-L-phenylalanine sodium, and L-tyrosine-O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-monosodium salt. The chemical structure of levothyroxine sodium is shown in FIG. **1**.

Administration of levothyroxine sodium provides T4 to a patient. Once absorbed by the organism, the administered T4 behaves identically to T4 that otherwise would be secreted by the thyroid gland of the patient, and binds to the same serum proteins, providing a supply of circulating T4-thyroglobulin in the patient. The administered T4 may be deiodinated in vivo to T3. As a result, a patient receiving appropriate doses of levothyroxine sodium will exhibit normal blood levels of T3, even when the patient's thyroid gland has been removed or is not functioning.

Levothyroxine sodium for injection is a sterile lyophilized product for parenteral administration of levothyroxine sodium for thyroid replacement therapy. Levothyroxine sodium for injection is particularly useful when thyroid replacement is needed on an urgent basis, for short term thyroid replacement, and/or when oral administration is not possible, such as for a patient in a state of myxedema coma.

Conventional formulations of levothyroxine sodium for injection are preservative-free lyophilized powders containing synthetic crystalline levothyroxine sodium and the excipients mannitol, tribasic sodium phosphate, and sodium hydroxide. These conventional formulations typically contain 10 milligrams (mg) of mannitol, 700 μg of tribasic sodium phosphate, and either 200 μg or 500 μg of levothyroxine sodium. Administration of the conventional formulation involves reconstitution of the lyophilized powder in 5 milliliters (mL) of 0.9% sodium chloride injection (USP), to provide injectable solutions having levothyroxine sodium concentrations of 40 micrograms per milliliter (μg/mL) or 100 μg/mL, respectively.

It is desirable to provide a new formulation of levothyroxine sodium that can further improve the stability of the levothyroxine. Preferably a new formulation of levothyroxine sodium would have acceptable stability above room temperature for an extended period of time. It is also desirable for the new formulation to be convenient to store, to reconstitute, and to administer to a patient.

SUMMARY

A composition is provided that includes from 100 to 500 micrograms of levothyroxine sodium, and from 1 to 5 milligrams mannitol. The composition is a solid.

A composition is provided that includes from 100 to 200 micrograms of levothyroxine sodium, and mannitol. The mass ratio of mannitol to levothyroxine sodium is at most 40:1, and the composition is a solid.

A composition is provided that includes about 500 micrograms of levothyroxine sodium, and mannitol. The mass ratio of mannitol to levothyroxine sodium is at most 10:1, and the composition is a solid.

A plurality of compositions is provided, where each composition includes from 100 to 500 micrograms of levothyroxine sodium and from 1 to 5 milligrams mannitol, and each composition is a solid. The amount of levothyroxine sodium in each composition spans the range of 100 to 500 micrograms. The amount of mannitol is substantially the same in each composition. When the plurality of compositions is stored at 25° C., at most 0.20% of the levothyroxine sodium in each composition is converted to liothyronine over a period of 12 months.

A solid composition is provided, which is formed by a method that includes combining ingredients to form a liquid mixture, and lyophilizing the liquid mixture. The ingredients include a solvent, levothyroxine sodium, mannitol, and substantially no tribasic sodium phosphate.

A solid composition is provided, which is formed by a method that includes combining ingredients to form a liquid mixture, and lyophilizing the liquid mixture. The ingredients include a solvent, levothyroxine sodium, mannitol and dibasic sodium phosphate. The mass ratio of mannitol to levothyroxine sodium in the liquid mixture is at most 40:1.

To provide a clear and more consistent understanding of the specification and claims of this application, the following definitions are provided.

The term "mass ratio" of two substances means the mass of one substance (**S1**) relative to the mass of the other substance (**S2**), where both masses have identical units, expressed as **S1**:**S2**.

The term "lyophilizing" means removing from a solution or an emulsion one or more substances having the lowest

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