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(54) **Title**: CONTAINER FOR PHARMACEUTICAL USE FOR THE QUANTITATIVE RELEASE OF A SINGLE DOSE FOR ORAL ADMINISTRATION OF T3 AND T4 THYROID HORMONES IN SOLUTION

(57) **Abstract**: The present invention relates to a container for pharmaceutical use for the quantitative release of a single-dose for oral administration of the T3 and T4 thyroid hormones in solution, characterized by the fact of being formed with a plastic material having a Young's modulus between 10 and 80 MPa.

CONTAINER FOR PHARMACEUTICAL USE FOR THE QUANTITATIVE RELEASE OF A SINGLE DOSE FOR ORAL ADMINISTRATION OF T3 AND T4 THYROID HORMONES IN SOLUTION

FIELD OF THE INVENTION

The present invention relates to a method of administration of pharmaceutical formulations based on thyroid hormones, and the relative means to implement it.

PRIOR ART

The hormones produced by the thyroid cells are released into the blood stream and act on the body's metabolism by increasing oxygen consumption and heat production with an increase in body temperature, stimulate protein synthesis and make the nitrogen balance more positive, increase gluconeogenesis and glycogenolysis, and stimulate the synthesis, mobilization, and catabolism of cholesterol and lipids in general. The thyroid hormones increase the rate of oxidative cellular processes and regulate the metabolism of most tissues. In general, it has a predominantly anabolic effect at low doses, while it has a catabolic action at high doses. This biphasic action is evident in the metabolism of glycogen, proteins, and lipids.

In case of physiological deficiency, it is necessary to intervene with a therapy based on the administration of thyroid hormones. T3 (liothyronine, or O-(4-hydroxy-3-iodophenyl)-3,5-diiodo-L-tyrosine) and T4 (levothyroxine, or O-(4-hydroxy-3,5-diiodo phenyl)-3,5-diiodo-L-tyroxine are known thyroid hormones used, as such or in the form of sodium or hydrate salts, for various therapeutic applications and are obtained by synthesis or extraction from animal glands.

The therapeutic treatment of the deficiency of these hormones gives satisfactory results with the intake of T3 or T4 (or their respective sodium salts). In particular, T3 and T4 are used primarily in the treatment of hypothyroidism.

The thyroid hormone administration therapy can often last for the patient's entire life. The dosage must be individually determined. Generally, the initial dose is low. The amount is then gradually increased until the clinical evaluation and laboratory tests indicate that an optimal response has been obtained from the treated organism. The dose required to obtain this response is then maintained. The age and general

physical condition of the patient and the severity and length of the hypothyroidism symptoms determine the initial dose and the speed with which the dosage can be brought to the definitive level. It is particularly important to only increase the doses very gradually in patients with myxedema or with cardiovascular diseases to prevent the manifestation of angina, myocardial infarction or stroke.

For these reasons, T3 and T4, their respective sodium salts, and their combination (Liotrix) are administered orally, in particular through tablets that allow their administration to be adapted to the patient's individual situation through the control of their ingestion frequency and through the choice of the dosage units.

A precise dosage is extremely critical as an underdosage could lead to an insufficient response and therefore to hypothyroidism. On the other hand, an overdosage would lead to toxic manifestations of hyperthyroidism including heart pain, palpitations, or cardiac arrhythmias. In patients with coronary disease, even a small increase in the dose of levothyroxine could be dangerous.

Therefore, due to risks associated with overdosage or underdosage of thyroid hormones in general, it is absolutely critical that patients can rely on formulations that are reliable in terms of titer and bioavailability.

Liothyronine (T3) and levothyroxine (T4) are currently on the market as oral drops in addition to a solid oral form primarily including tablets and soft gelatin capsules.

The former is a single container of 20 ml equipped with a dropper. However, this dropper does not guarantee the precise measurement of provided volume that is desired. Calculating a content of approximately 3.5 µg of T4 for every drop, various intermediate dosages between 3.5 and 200 µg could in theory be obtained. The latter dosage is reached by aliquoting 2 ml with 56 drops (considering the minimum quantity of a drop). However, dispensing a high number of drops is not easy or safe; further, the drops are never dispensed at an identical volume in a repeatable way. Therefore, it is not generally possible to guarantee the dosing precision that is obtained with the individual formulation in tablets or soft capsules.

However, a significant advantage of the liquid formulation is the stability of the active ingredient for both T4 and for T3. Therefore, the ability to accurately deliver the

volume of a solution containing the effective dose of liothyronine T3 and levothyroxine T4 to administer while maintaining the ideal stability of the active ingredient is the problem to be resolved by this invention.

The plastic containers available today for pharmaceutical use, primarily polyethylene and polypropylene, are designed to dispense even viscous liquid by guaranteeing a minimum dispensable volume, but they do not permit the precision of the delivery. Even with single-dose bottles, the bottle does not allow a quantitative release of the contained dose, i.e. complete, but only the release of a minimum dose.

This may be acceptable in some therapeutic fields. A typical example are the soft vials for ophthalmic use, containing eye washes or eye drops.

Instead, this would not be acceptable for the case at hand, i.e. for thyroid hormones, for the dosage precision reasons cited above. Bottles of this type for the administration of thyroid hormones are not known, nor have they been proposed until now.

The purpose of this invention is therefore the solution of the technical problem described above.

SUMMARY OF THE INVENTION

To this end, a container for pharmaceutical use is proposed for the quantitative release of a single-dose for oral administration of the T3 and T4 thyroid hormones in solution, characterized by the fact of being formed with a plastic material having a Young's modulus between 10 and 80 MPa.

DETAILED DESCRIPTION OF THE INVENTION

Therefore, according to the invention, suitable plastic materials are those which can be formed with a Young's modulus that is sufficiently low and within the critical range defined above. It has in fact been found that the selection of this critical parameter allows an almost complete emptying, or extraction, of the T3 and T4 thyroid hormones solution under compression from a container containing them, such as a bottle, made of that material.

This selection may be considered as surprising given the very high values of the Young's modulus in known plastic containers for pharmaceutical use, primarily

polyethylene or polypropylene, for example single-dose bottles for ophthalmic use containing eye washes or eye drops, as will soon be described with reference to the following table.

For the determination of the Young's modulus for the purposes of this invention, samples of sizes determined by the UNI-EN-ISO 527-1 reference standard were used, subjected to traction with a traction velocity of 5 mm/min.

According to a first embodiment of this invention, plastic materials with this Young's modulus can be obtained by injection molding. In case an injection mold is used, the Young's modulus of the suitable plastic materials is generally between 30 and 80 MPa.

Suitable plastic materials are chosen from mixtures of polyethylene (PE) or polypropylene (PP) with ethylene-vinyl acetate (EVA).

PE/EVA mixes are preferred choices in the range between PE 15% + EVA 85% and PE 35% + EVA 65%.

The Young's modulus derived for two different materials according to the invention is reported in the following table for comparative purposes, defined as Mix 50 PE / 50 EVA = PE 50% + EVA 50%, and Mix 25 PE / 75 EVA = PE 25% + EVA 75%, compared to samples formed with a material for bottles according to the known technique, i.e. only polypropylene (PP) and only low-density polyethylene (LDPE).

TABLE

Young's Modulus / traction velocity of 5 mm/min (UNI-EN-ISO 527-1)

SAMPLE	Young's Modulus (MPa)
PP	100.7 ± 3.3
LDPE	92.9 ± 3.5
50 PE / 50 EVA Mix	63.5 ± 3.4
25 PE / 75 EVA Mix	42.2 ± 5.1

According to a further embodiment of this invention, plastic materials with a suitable Young's modulus include gelatin and mixtures thereof. The Young's modulus is generally between 10 and 50 MPa in this case.

Plastic materials with a suitable Young's modulus in this case can be obtained with rotary-die process molding suitable for the production of soft gelatin capsules.

In this case, the T3 and T4 thyroid hormone solution is injected within the gelatin-based plastic material in the form of a gelatinous semi-finished product in the fusion state, in order to create soft capsules; the formation of a sealable opening for the delivery of the solution will be provided within the said soft capsule.

According to the invention, it is necessary in this case to mix the gelatin, for example animal gelatin, with substances that make the gelatin insoluble in or impermeable to water, such as cyclodextrins and dimethicone. Polyvinyl alcohol (PVA), polyacrylates or aluminum glycinate are useful substances for making the gelatin insoluble in water.

Other processes known and described in the pharmaceutical literature for the production of soft elastic capsules (SEC) with liquid or semi-liquid content, such as the "Plate Process" or the use of the "Norton Capsule Machine" or the "Accogel Capsule Machine" as in "Remington's Pharmaceutical Sciences", 18th edition, edited by Alfonso R. Gennaro, 1990, Mack Publishing Company, Easton Pennsylvania 18042, ISBN 0-912734-04-3, are applicable for the production of containers in the form of soft capsules according to this invention including thyroid hormones and any excipients in a liquid or semi-liquid carrier.

In the choice of plastic materials suitable for the purposes of this invention, in addition to the Young's modulus selected in the critical way as described above, the surface energy of the material, according to the Owens Wendt method, should preferably be maintained under 36 mN/m. The allows the wettability of the container by the T3 and T4 thyroid hormones solution, which must flow within it during the delivery, to be controlled in an ideal way, and therefore the capacity for flow along the inner wall.

For an indicative and not limiting purpose, the total surface energy values γ, expressed in mN/m, are stated for the mixes of plastic materials of the invention

specified in the above table.

50 PE / 50 EVA Mix γ = 31.3 mN/m

25 PE / 75 EVA Mix γ = 34.1 mN/m

The characteristics and advantages of this invention will be described in detail in the following description.

The following examples of the present invention are reported for illustrative and not limitative purposes.

Comparative example 2 is reported for purposes of comparison as an example using the known technique.

EXAMPLE 1

Preparation of a glycerol-ethanol solution of levothyroxine sodium (T4)

Components and quantities for a preparation of 25 liters:

Levothyroxine sodium (T4) 2.625 g

Glycerol (85%) 21.525 kg

Ethanol (96%) 6.100 kg

In a steel container of 10 liters equipped with a blade stirrer and cover, add 90% of the ethanol (5.49 liters) and add the T4 while stirring; stir slowly while maintaining a flow of nitrogen until complete dissolution. In a 25 liter turboemulsifier (Olsa-Italy), pour in the glycerol (21.525 kg) and add the ethanol solution containing the T4 solution. Wash the 10-liter container with the remaining ethanol (0.61 liters) and pour it into the 25-liter turboemulsifier. Continue stirring at low speed for 15 minutes under nitrogen and protected from light.

COMPARATIVE EXAMPLE 2

Preparation of neutral LDPE single-dose plastic containers, of 1.0 ml nominal (1.3 ml filling volume) with a screw cap containing the glycerol-ethanol solution of levothyroxine sodium (T4).

a) preparation of single-use containers

Material, quantity for preparation and relative percentage composition:

Low-density polyethylene (LDPE) 50.0 Kg 100 %

The product consists of a strip of 5 1.0 ml single-doses with screw cap.

The strip of 5 single-doses and the strip of 5 caps are produced by injection molding with two different molds, and are then assembled with semi-automatic equipment.

The characterization of the molder products is carried out through determination of the Young's modulus: samples of sizes determined by the UNI-EN-ISO 527-1 reference standard are used, and subjected to traction with a traction velocity of 5 mm/min.

LDPE	92.9 MPa

b) preparation of the T4 solution

The glycerol-ethanol solution obtained according to example 1 is used.

c) Filling of the single-use containers

The containers obtained in a) are filled with 1.05 ml of glycerol-ethanol solution described in b) by automatic pipette (Gilson P-1000), then sealed with a Pentaseal-lab model bench-top sealer (Lameplast - Rovereto di Modena - Italy).

The emptying test of a container according to c) has provided a percentage extractability of the solution with respect to theory equal to 90%.

EXAMPLE 3

Preparation of neutral LDPE/EVA single-dose plastic containers, of 1.0 ml nominal (1.3 ml filling volume) with screw cap containing the glycerol-ethanol solution of levothyroxine sodium (T4).

a. preparation of the single-use containers

Material, quantity for preparation and relative percentage composition:

Low-density polyethylene (LDPE) 25.0 kg 50 %

ethylene-vinyl acetate (EVA) 25.0 kg 50 %

The product consists of a strip of 5 1.0 ml single-doses with screw cap.

The strip of 5 single-doses and the strip of 5 caps are produced by injection molding with two different molds, and are then assembled with semi-automatic equipment.

The characterization of the molder products is carried out through determination of the Young's modulus: samples of sizes determined by the UNI-EN-ISO 527-1 reference standard are used, and subjected to traction with a traction velocity of 5

mm/min. The following is measured:

50 LDPE / 50 EVA Mix	63.5 MPa

The total surface energy γ of the material, evaluated according to the Owens Wendt method, was also measured:

50 PE / 50 EVA Mix γ = 31.3 mN/m

b) preparation of the T4 solution

The glycerol-ethanol solution obtained according to example 1 is used.

c) Filling of the single-use containers

The containers obtained in a) are filled with 1.05 ml of glycerol-ethanol solution described in b) by automatic pipette (Gilson P-1000), then sealed with a Pentaseal-lab model bench-top sealer (Lameplast - Rovereto di Modena - Italy).

The emptying test of a container according to c) has provided a percentage extractability of the solution with respect to theory equal to 96%.

EXAMPLE 4

Preparation of neutral LDPE/EVA single-dose plastic containers, of 1.0 ml nominal (1.3 ml filling volume) with screw cap containing the glycerol-ethanol solution of levothyroxine sodium (T4).

b. preparation of the single-use containers

Material, quantity for preparation and relative percentage composition:

Low-density polyethylene (LDPE) 12.5 kg 25 %

ethylene-vinyl acetate (EVA) 37.5 kg 75 %

The product consists of a strip of 5 1.0 ml single-doses with screw cap.

The strip of 5 single-doses and the strip of 5 caps are produced by injection molding with two different molds, and are then assembled with semi-automatic equipment.

The characterization of the molder products is carried out through determination of the Young's modulus: samples of sizes determined by the UNI-EN-ISO 527-1 reference standard are used, and subjected to traction with a traction velocity of 5 mm/min. The following is measured:

25 LDPE / 75 EVA Mix	42.2 MPa

The total surface energy γ of the material, evaluated according to the Owens Wendt method, was also measured:

25 PE / 75 EVA Mix γ = 34.1 mN/m

b) preparation of the T4 solution

The glycerol-ethanol solution obtained according to example 1 is used.

c) Filling of the single-use containers

The containers obtained in a) are filled with 1.05 ml of glycerol-ethanol solution described in b) by automatic pipette (Gilson P-1000), then sealed with a Pentaseal-lab model bench-top sealer (Lameplast - Rovereto di Modena - Italy).

The emptying test of a container according to c) has provided a percentage extractability of the solution with respect to theory equal to 98%.

EXAMPLE 5

Preparation of single-dose plastic containers in the form of openable soft gelatin capsules containing T4 in ethylene glycol and ethanol solution.

a) preparation of the mixture for the container's casing

Components, quantity for preparation and relative percentage composition:

Gelatin 150 bloom 28.0 kg 35.0%

Sorbitol (special polyol solution) 5.6 kg 7.0%

Dimethicone 1000 24.0 kg 30.0%

Purified water 22.4 kg 28.0%

In a 150-liter turboemulsifier (Olsa-Italy), 5.6 kg of special sorbitol and 24 kg of dimethicone are added to 22.4 kg of purified water. Vigorous stirring is maintained and the temperature is brought to 70 °C, and then 28 kg of gelatin are added and maintained under stirring for 15-60 minutes. The mass is then deaerated by applying a progressive vacuum until reaching a value between –0.8 and -0.9 bar. The mixture obtained is unloaded and stored, until the encapsulation, at the appropriate

temperature, between 50°C and 70°C.

b) preparation of the T4 solution

The glycerol-ethanol solution obtained according to example 1 is used.

c) preparation of the container with solution in the form of soft capsules

Soft gelatin capsules with an 8-tube format (or twist-off) were prepared according to the following known Rotary Die type process.

The gelatinous mixture prepared according to a) is transferred by nitrogen pressure to two thermostated (50°C / 70°C) spreader boxes, from which it drips on two rollers cooled to 18°C±5°C, allowing the formation of gelatin ribbons of a predetermined thickness.

The two gelatin ribbons are accompanied to the sides of the solution injection segment and through two molds. In this phase, the injection pump operates the filling with the solution according to b) allowing the formation of the capsules.

The solution according to b) is injected in the measure of 1 ml, in capsules of an 8-tube format, whose sealing is guaranteed by the combined and simultaneous pressure of the molds, the heating of the injection segment, and the ribbons (partial fusion).

The capsules formed are transferred to special tumble driers where they begin the water loss phase, completed after a pause in the desiccation tunnel for the achievement of a moisture content between 5% and 15%.

Openable soft gelatin capsules having the following characteristics are thus obtained:

average weight per capsule: 745 mg ±7.5%

residual moisture: 1.0%

T4 content: 0.050 mg/capsule, equal to 100.0% d.d.

hardness: 6-10 N

Young's modulus: between 10 and 50 MPa.

The emptying test of a soft capsule container according to this example has provided a percentage extractability of the solution with respect to theory equal to 98%.

As can be understood from the entire description reported above, the invention allows the achievement of a nearly quantitative release of a predetermined dose of thyroid

hormones T3 and T4 in solution for oral administration, thus effectively achieving the originally proposed purpose.

CLAIMS

1. A container for pharmaceutical use for the quantitative release of a single-dose for oral administration of the T3 and T4 thyroid hormones in solution, characterized by the fact of being formed with a plastic material having a Young's modulus between 10 and 80 MPa.
2. The container according to claim 1, characterized by the fact of being obtained by injection of a plastic material having a Young's modulus between 30 and 80 MPa.
3. The container according to claim 2, characterized by the fact of being obtained by injection of a plastic material chosen between mixes of polyethylene (PE) or polypropylene (PP) with ethylene-vinyl acetate (EVA).
4. The container according to claim 3, characterized by the fact that these PE/EVA or PP/EVA mixes are chosen in the range between PE or PP 15% + EVA 85%, and PE or PP 35% + EVA 65%.
5. The container according to claim 4, characterized by the fact that these PE/EVA mixes are the following:

Material	Young's Modulus (MPa)
Mix 50% PE / 50%EVA	63.5 ± 3.4
Mix 25% PE / 75% EVA	42.2 ± 5.1

6. The container according to claim 1, characterized by the fact that said material is gelatin or mixes of it, and that said Young's modulus is between 10 and 50 MPa.
7. The container according to claim 6, characterized by the fact that said plastic material is a mix of gelatin with water and with one or more substances, including agents that make the gelatin itself insoluble or impermeable to water.

8. The container according to claim 7, characterized by the fact that said agents that make the gelatin insoluble or impermeable to water are chosen among cyclodextrins, dimethicone, polyvinyl alcohol (PVA), polyacrylates, and aluminum glycinate.
9. The container according to claim 7, characterized by the fact that said plastic material is a mix of gelatin, Sorbitol, Dimethicone, and water.
10. The container according to claim 1, characterized by the fact that said material has a surface energy under 36 mN/m.
11. A method for the preparation of a single-dose for oral administration of T3 and T4 thyroid hormones in solution within a container according to claim 6, characterized by the fact that said solution is injected within the gelatin-based plastic material in the gelatinous semi-finished form in the fusion state to give a soft capsule according to the rotary die process; a sealable opening for the delivery of said solution for administration being provided in said soft capsule.
12. A solution of T3 and T4 thyroid hormones for oral administration prepared in a single-use container according to the method of claim 11.
13. A single-dose for the quantitative oral administration of a solution of T3 and T4 thyroid hormones, characterized by the fact of being contained in a container made with a plastic material having a Young's modulus between 10 and 80 MPa and that can therefore be completely emptied.
14. The single-dose for the quantitative oral administration of a solution of T3 and T4 thyroid hormones according to claim 13, characterized by the fact of being contained in a container made with a plastic material having a Young's modulus between 10 and 80 MPa and a surface energy less than 36 mN/m.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61J3/07 A61K9/48
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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)
A61J A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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