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The effect of excipients on the stability of levothyroxine sodium pentahydrate tablets

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Abstract

Levothyroxine tablets, 50 μg, have been marketed for many decades but have had numerous recalls due to degradation and failure to meet potency. These experiments were devised to study the effects of various excipients on the stability of levothyroxine sodium pentahydrate in aqueous slurries and in formulated tablets. The active alone was found to be stable in the solid state for 6 months at 40 °C/75% RH whether stored in open or closed containers, and was found to be non-hygroscopic under normal processing conditions (>30% RH). In aqueous slurries with an excipient, the stability of the active improved as the pH of the slurry was increased from pH 3 to 11. Tablets manufactured with lactose anhydrous, starch, or microcrystalline cellulose failed to meet USP assay requirements at 3 months at 40 °C/75% RH. Tablets manufactured with dibasic calcium phosphate or mannitol met USP assay requirements at 3, but not 6 months when stored at 40 °C/75% RH. Tablets manufactured with dibasic calcium phosphate and a basic pH modifier, such as sodium carbonate, sodium bicarbonate, or magnesium oxide, met the USP assay requirements at both 3 and 6 months. Thus, the use of basic pH modifiers is a potential technique for improving the stability of levothyroxine sodium pentahydrate tablets.

Keywords: Levothyroxine sodium; Tablets; Excipient; Stability; Slurries; pH modifiers

1. Introduction

Levothyroxine sodium pentahydrate (Scheme 1) is the sodium salt of the levo-isomer of thyroxine, an active physiological substance found in the thyroid gland. It has three ionizable moieties: carboxyl group ($pK_a = 2.4$), phenolic group ($pK_a = 6.87$) and amino group ($pK_a = 9.96$). The aqueous solubility of levothyroxine reduces from pH 1 to 3, remains constant from 3 to 7, and significantly increases above pH ∼7 (Won, 1992; Post and Warren, 1976). Synthetic levothyroxine is used primarily in the treatment of hypothyroidism and as a thyroid stimulating hormone (TSH) suppressant, in the treatment or prevention of various types of euthyroid goiters (Goodman and Gilman, 2001).

The first synthetic levothyroxine product was introduced in the United States in 1955 by Flint under the brand name Synthyroid®, without an approved "New Drug Application" (NDA) apparently in the belief that it was not a new drug substance. Since then, there have been frequent recalls of levothyroxine tablets by

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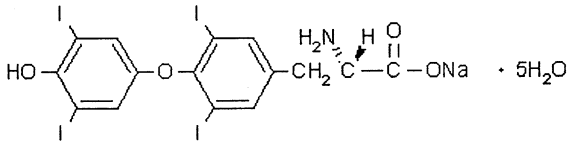

Scheme 1. Levothyroxine sodium pentahydrate.

multiple companies for millions of tablets. With few exceptions, all the recalls were initiated due to the discovery of tablets being sub-potent before the labeled expiration date or lack of assurance that product will maintain potency until the respective expiration date (Rhodes, 1998). This lack of stability and inconsistent potency has the potential to cause serious health consequences to those requiring levothyroxine.

Now, more than 40 years after introduction into the market, the U.S. Food and Drug Administration (FDA) has issued notice that orally administered drug products containing levothyroxine are officially classified as "new drugs" and will be subject to the NDA submission process.

According to the Federal Register Notice, "no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability, and thus, no currently marketed orally administered levothyroxine sodium product is generally recognized as safe and effective" (Federal Register, August 14, 1997).

Because the drug is required by millions of patients, the FDA allowed manufacturers to continue to market these products without approved NDAs until 14 August 2000. This date was extended to 14 August 2001, at which time, there were only two levothyroxine products (Unithyroid® and Levoxyl®) with approved NDAs having a shelf life of 18 months. The FDA has issued a guideline for manufacturers, who are unable to obtain an NDA or ANDA approval, in order for them to withdraw their products (FDA, 2001).

Levothyroxine has a complex stability profile and is sensitive to light, temperature, moisture, pH and oxidation (Post and Warren, 1976; Won, 1992; Kazemifard et al., 2001; Garnick et al., 1984; Wortsman et al., 1989). Won (1992) studied the kinetics of degradation of levothyroxine sodium in solution and in solid state. He concluded that in solution levothyroxine sodium followed first order kinetics of degradation. It was found that as the pH of the solution was increased, the degradation reduced. The proposed degradation pathway was deiodination. Solid state degradation kinetics were found to be bi-phasic and the proposed pathway was by deamination.

Rhodes (1998) reported that levothyroxine tablets stability is a complex problem and a scientific study of the degradation process would result in the use of appropriate formulation and processing methods, which would effectively remove current problems. The above statement might shed light on some of the factors that have been associated with the current problems associated with commercial levothyroxine tablets. For a highly potent low dose drug (like levothyroxine), significant degradation is expected for the active contained in the drug product because of high excipient content (Badaway et al., 1999).

Thus, the purpose of this study was to determine the effect of excipients on the stability of levothyroxine sodium pentahydrate and its corresponding tablets.

2. Materials and methods

2.1. Materials

The following materials were used: levothyroxine sodium pentahydrate (ACROS Organics, Fair Lawn, NJ, USA), dibasic calcium phosphate (Emcompress®, Penwest, Patterson, NY, USA), lactose anhydrous (Quest International, Norwich, NY, USA), ATLAS® mannitol (ICI Americas, Inc., Wilmington, DE, USA), microcrystalline cellulose (MCC) (Emcocel® 90M, Penwest, Patterson, NY, USA) and Starch® 1500 (Colorcon, West Point, PA, USA), magnesium stearate (Mallinckrodt Chemical Inc., St. Louis, MO, USA), aluminum lake blue # 2 (Colorcon), Povidone (Kollidon 30 (PVP), BASF), hydroxypropyl methycellulose (HPMC, Methocel® K100LV, Dow Chemical Co., Midland, MI, USA), croscarmellose sodium (AcDiSol®, FMC Corporation, Newark, DE, USA), sodium starch glycolate (Explotab®, Penwest, Patterson, NY, USA), crospovidone (BASF, Ludwigshafen, Germany), stearic acid (Mallinckrodt Chemical Inc.), fumed silica (Cab-O-Sil® M-5P, Cabot Corporation, Tuscola, IL, USA), HYDRANAL® Composite 2 & HYDRANAL® Methanol (Aldrich Chemical Company, Milwaukee, WI, USA). The acetonitrile (HPLC), water (HPLC), trifluoroacetic acid, phosphoric acid,

triiodo-L-thyronine, sodium hydroxide, hydrochloric acid, sodium carbonate, sodium bicarbonate, magnesium oxide, tartaric acid and citric acid were all obtained from Fisher Scientific (Fair Lawn, NJ, USA). Diiodo-L-thyronine, tetraiodothyroacetic acid, triiodothyroacetic acid and diiodothyroacetic acid were obtained from Sigma Chemical Co. (St. Louis, MO, USA). High density polyethylene bottles (HDPE) (SETCO Inc., Anaheim, CA, USA) were used for storing tablets.

2.2. Equipment

A Beckman System Gold® 126 Solvent Module HPLC with UV detector (Beckman Coulter, Fullerton, CA, USA) and a Cyano-Spherisorb HPLC Column (Water Corp., Milford, MA, USA.) was used to perform assays. Mass spectroscopy was performed using a Micromass mass spectrophotometer (Micromass LTD, UK) with electro-spray ionization. A Karl Fisher moisture analyzer (Metrohm, Switzerland) was used to determine the moisture in the samples, and a moisture sorption balance (VTI Corporation, Hialeah, FL, USA) was employed to determine the hygroscopicity of the active drug substance. The tablets were compressed with a Carver laboratory press (Fred S. Carver Inc., Menomonee Falls, WI, USA) and stored at accelerated stability conditions in an Espec humidity cabinet LHL112 (Tabai Espec Corp., Osaka, Japan). The pH of slurries was tested using a flat-surface pH meter (PH 900®, Courage-Khazaka, Köln, Germany).

2.3. Methods

2.3.1. Assay

An HPLC system equipped with an auto sampler and a UV detector set at 225 nm was used for the analysis of all samples (Garnick et al., 1984). The reversed phase HPLC assay method used a Waters® Spherisorb Cyano, 25 cm × 2 mm column (particle size 5 μm) and a acetonitrile:water mixture (40:60) with 0.5 ml/l phosphoric acid as mobile phase at a flow rate of 0.3 ml/min. For the analysis of samples of tablets manufactured with pH modifiers, the phosphoric acid in the mobile phase was replaced with (0.3 ml/l) trifluoroacetic acid as this enhanced the recovery of levothyroxine. Spiked levothyroxine samples with various degradation products, namely, triiodo-L-thyronine, diiodo-L-thyronine, tetraiodothyroacetic acid, triiodothyroacetic acid and diiodothyroacetic acid were injected to test the methods (Garnick et al., 1984).

2.3.2. Moisture determination

Moisture content in samples was determined by Karl Fisher titration according to USP titrimetric method for water determination. Approximately 100 mg of each powdered sample was titrated with the Karl Fisher reagent, HYDRANAL® Composite 2.

2.3.3. Stability and hygroscopicity of levothyroxine sodium pentahydrate

Levothyroxine sodium pentahydrate powder was stored in open and closed vials at 40 °C and 75% RH (ICH Q1A(R), 2000; FDA, 1998) for a total of 6 months. Assay and moisture determination was performed at 0, 3 and 6 months. The hygroscopicity of levothyroxine sodium pentahydrate was determined with a moisture sorption balance. Levothyroxine sodium pentahydrate was placed on the weighing tray and the relative humidity in the environment was increased gradually, in 5% RH increments from 30 to 100% RH, after allowing the necessary time for the sample stabilization, up to 2 h, at each period. Subsequently, the humidity was gradually reduced to 10% RH in a similar manner.

2.3.4. Stability of levothyroxine sodium pentahydrate slurries

2.3.4.1. With different excipients. The stability of levothyroxine sodium pentahydrate in slurries was tested in the presence of the following excipients: HPMC, povidone, croscarmellose sodium, sodium starch glycolate, crospovidone, stearic acid, magnesium stearate and fumed silica. Five percent of each of the above excipients individually was mixed with 95% dibasic calcium phosphate. Since under usual conditions of formulation the above-mentioned excipients are found in low concentrations, for this study, the excipients were added at 5% of the solid content. Dibasic calcium phosphate was chosen, as it was found as one of the most inert diluents during preliminary studies. The above powder blends were mixed with water to make 20% (w/v) aqueous slurries.

2.3.4.2. With different excipients at different pH. The stability of levothyroxine sodium pentahydrate in slurries was tested with different excipients at different pH. Twenty percent (w/v) aqueous slurries were prepared using each of the following excipients: microcrystalline cellulose, mannitol, starch or dibasic calcium phosphate. For each excipient the pH of the slurries were adjusted to 3, 5, 7, 9 and 11 using 0.1N HCl or 0.1N NaOH. Additional slurries were prepared for each excipient without pH adjustment. The pH values of all the slurries were verified by means of a pH meter outfitted with a flat-surface electrode.

For all the slurries, levothyroxine solution was added to obtain a final drug concentration of 4 μg/ml. Slurries were assayed at time 0 and after 1-month storage at 50 °C. The study was performed with levothyroxine in solution to maximize its availability for reaction. Won (1992) suggested that there exists a threshold temperature between 50 and 60 °C where levothyroxine sodium degrades rapidly. At 50 °C, little degradation was observed in the solid state up to 30 days. At temperatures of 60 °C or greater, solid-state degradation kinetics were found to be biphasic. Therefore, the temperature these experiments was set at 50 °C.

2.3.5. Stability of levothyroxine sodium pentahydrate tablets

2.3.5.1. Manufactured with different diluents. Different batches of 50 μg levothyroxine sodium pentahydrate tablets were manufactured using one of the following five diluents: lactose anhydrous, microcrystalline cellulose, mannitol, starch and/or dibasic calcium phosphate. All tablets contained magnesium stearate and aluminum lake blue # 2 (Table 1).

2.3.5.2. Manufactured with pH modifiers. Different batches of 50 μg levothyroxine sodium pentahydrate tablets were manufactured with dibasic calcium phosphate and different basic pH modifiers, namely sodium carbonate, sodium bicarbonate and magnesium oxide, and acidic pH modifiers, namely, tartaric acid and citric acid. The pH of the saturated solution of each of the pH modifiers used is: 8.1, 11.9, 10.3, 1.7 and 0.4 for sodium bicarbonate, sodium carbonate, magnesium oxide, tartaric acid, and citric acid, respectively (this would correspond to the approximate microenvironmental pH). A batch of tablets with no pH modifier served as a control (Table 1).

Table 1
Composition (%, w/w) of levothyroxine sodium pentahydrate 50 μg tablets

Ingredients	Tablets with different diluents (%)	Tablets with pH modifiers (%)
Levothyroxine sodium pentahydrate	0.05	0.05
Aluminum lake blue # 2	0.05	0.05
Magnesium stearate	1.00	1.00
Diluent[a]	98.9	–
pH modifiers[b]	–	10.00
Dibasic calcium phosphate	–	88.90

[a] Each of the following five diluents: lactose anhydrous, microcrystalline cellulose, mannitol, starch or dibasic calcium phosphate.
[b] Each of the following five pH modifiers: sodium carbonate, sodium bicarbonate, magnesium oxide, tartaric acid and citric acid.

For all the tablets, the ingredients, according to the ratios listed in Table 1, were mixed by geometric dilution in a mortar and pestle and directly compressed at 1000 lb using a Carver press. Tablets were stored in HDPE bottles with and without desiccant. The batches were tested for uniformity of dosage units (USP 25). The stability of the tablets was evaluated for 6 months under ICH accelerated stability conditions (40 °C and 75% RH). Assay and moisture determination were performed at 0, 3 and 6 months after storage.

For the tablets manufactured with different diluents (a), mass spectroscopy was performed on the 6-month samples, which exhibited degradation, to identify degradation products/pathways. The 3-month samples were analyzed for racemization by the same assay procedure using a chiral crown ether column (prepared in-house) (Jin et al., 2001).

3. Results and discussions

3.1. Stability and hygroscopicity of levothyroxine sodium pentahydrate

Levothyroxine sodium pentahydrate drug substance was found to be stable when stored for 6 months at accelerated stability conditions (40 °C/75% RH) in an open or closed containers with assay values of 97.5 and 97.1%, respectively (Table 2).

Table 2
Effect of diluents on the stability of levothyroxine tablets stored at 40 °C/75% RH for 6 months

Diluent	Months		
	0	3	6
Uncompressed pure drug in open vial	100.0 (9.6)[a]	99.2	97.5 (10.2)[a]
Uncompressed pure drug in closed vial	100.0 (9.6)[a]	102.2	97.1 (9.8)[a]
Microcrystalline cellulose[b]	100.0 (6.2)[a]	79.4 (5.9)[a]	70.7 (6.5)[a]
Starch[b]	100.0 (7.8)[a]	81.3 (7.7)[a]	73.3 (10.25)[a]
Dibasic calcium phosphate[b]	100.0 (0.5)[a]	91.9 (0.5)[a]	85.3 (0.8)[a]
Lactose anhydrous[b]	100.0 (0.8)[a]	86.9 (2.5)[a]	68.7 (5.0)[a]
Mannitol[b]	100.0 (0.3)[a]	90.3 (0.4)[a]	86.9 (0.6)[a]

[a] Percent recovery of levothyroxine/(% moisture).
[b] Each 100 mg tablet containing 50 μg levothyroxine sodium pentahydrate and 98.9 mg of the above-mentioned excipient.

Levothyroxine sodium pentahydrate shows little moisture gain (∼1%) from 30 to 90% relative humidity in the moisture adsorption–desorption study (Fig. 1). It lost moisture (3.5% weight change) rapidly from 30 to 10%. The total moisture/water content of levothyroxine sodium pentahydrate determined by Karl Fisher moisture determination is 9.6%, which is reasonably consistent with the theoretical contribution of water from pentahydrate, calculated to be 10.1%, and is consistent with that reported by Post and Warren (1976).

This indicates levothyroxine sodium pentahydrate is non-hygroscopic under normal processing conditions (RH > 30%) and below this, it looses moisture.

3.2. Effect of excipients and pH on the stability of levothyroxine sodium pentahydrate in slurries

Different excipients influenced the stability of levothyroxine sodium pentahydrate in slurries to varying extents. Levothyroxine assay values of the various slurries after storage at 50 °C for 1 month were as follows: with crospovidone—37.2%, with stearic acid—62.3%, with sodium starch glycolate—77.9%, with povidone—77.9%, with croscarmellose sodium—83.1%, with HPMC—84.9%, with fumed silica—89.9%, with magnesium stearate—95.7% and dibasic calcium phosphate (no additional excipient)—86.7% (Fig. 2).

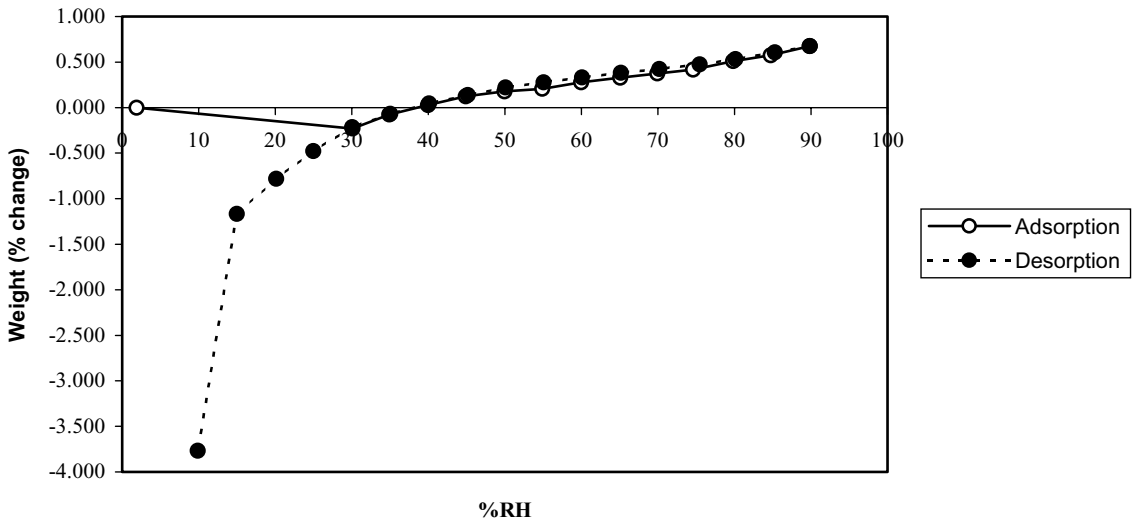

Fig. 1. Adsorption–desorption isotherm of levothyroxine sodium pentahydrate.

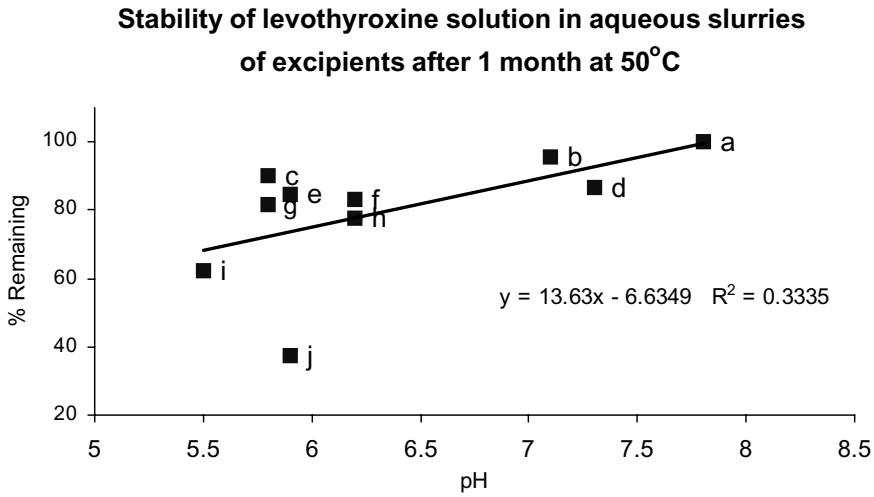

Fig. 2. Stability of levothyroxine (in solution) in 20% (w/v) aqueous slurries containing 5% excipient + 95% dibasic calcium phosphate. Initial drug concentration = 4 μg/ml. Excipients (a) drug alone, (b) magnesium stearate, (c) fumed silica, (d) dibasic calcium phosphate, (e) HPMC, (f) croscarmellose sodium, (g) povidone, (h) sodium starch glycolate, (i) stearic acid, and (j) crospovidone.

It was found that pH influenced the stability of levothyroxine sodium pentahydrate in excipient slurries. In all the excipient slurries levothyroxine sodium pentahydrate showed more degradation at pH 3 than at pH 11 (Fig. 3). Levothyroxine assay value for the various slurries at pH 11 ranged from 89 to 96% versus 70–87% for slurries with no pH modification and 49–68% for the slurries at pH 3 after storage at 50 °C for 1 month. For each excipient, levothyroxine sodium pentahydrate stability in slurries improved, as the pH increased from acidic to basic. This inferred that the addition of a basic pH modifier improves the stability of levothyroxine sodium pentahydrate in the presence of various excipients.

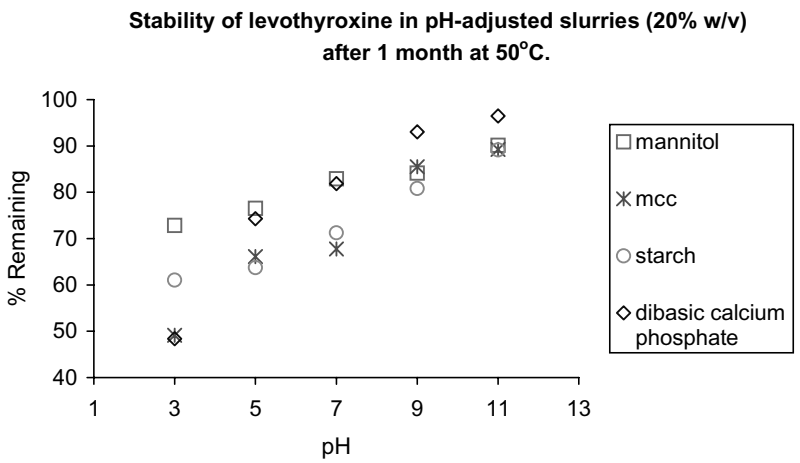

Fig. 3. Stability of levothyroxine (in solution) in aqueous slurries containing 20% (w/v) excipient. Initial drug concentration = 4 μg/ml. The pH of the slurries was adjusted with 0.1N HCl or NaOH. The stability and native pH of the pH-unadjusted slurries were found to be 75.6% (mannitol, pH 5.3), 72.6% (microcrystalline cellulose, pH 5.5), 70.4% (starch, pH 6.2), and 87.1% (dibasic calcium phosphate, pH 7.3).

3.3. Effect of excipients on the stability of levothyroxine sodium pentahydrate tablets

As shown in Table 2, the best stability of levothyroxine sodium pentahydrate, was achieved when mannitol or dibasic calcium phosphate was used as the tablet diluent. After 6 months at 40 °C/75% RH, tablets prepared with these diluents had a significantly lower moisture content (<1%) compared to tablets prepared with microcrystalline cellulose, starch, or lactose anhydrous (≥5%). Nevertheless, these tablets did not meet USP assay requirements for potency at 6 months under accelerated conditions. This implies that while moisture control improves stability, it is not enough to ensure a stable formulation.

The primary degradation pathways observed by mass spectroscopy were deiodination and deamination. These findings were consistent with the previous findings of Andre et al. (1996), and Kazemifard et al. (2001). Decarboxylation products were also observed. No racemization was observed for any of the tablet batches.

It was concluded that the type of diluent used in the manufacture of levothyroxine sodium pentahydrate tablets affects its stability. Thus, the study and proper choice of excipients in the manufacturing of levothyroxine sodium pentahydrate tablets were critical. Although lactose and microcrystalline cellulose are the most commonly used diluents in currently marketed levothyroxine products, they did not prove to be the most suitable diluents in this study.

This is in agreement with Gupta et al. (1990) who studied levothyroxine tablets from two different manufacturers. They observed that tablets from the same manufacturer may have lot to lot variation of the excipients. They also observed that tablets from a particular manufacturer contained excipient(s) that act as a catalyst to hasten decomposition.

The pH of saturated solutions of the powdered levothyroxine sodium tablets ranged from 5.5 to 7.3, while the pH of saturated solution of levothyroxine sodium was 8.0. Thus, the inherent pH of the microenvironment found in the compressed tablets did not coincide with the pH of maximum stability of levothyroxine sodium pentahydrate. This may explain why levothyroxine sodium pentahydrate drug substance alone was more stable than levothyroxine sodium pentahydrate in tablets (Table 2).

3.4. Effect of pH modifiers on levothyroxine sodium tablets

In the presence of dibasic calcium phosphate and a basic additive, the stability of the levothyroxine sodium pentahydrate tablets was improved. The 6-month assay values of levothyroxine in tablets manufactured with dibasic calcium phosphate and sodium carbonate, sodium bicarbonate, magnesium oxide, tartaric acid or citric acid were 95.2, 94.7, 96.8, 78.3 and 74.4%, respectively. Levothyroxine sodium pentahydrate tablets containing basic pH modifiers, namely sodium carbonate, sodium bicarbonate or magnesium oxide met USP assay requirements (90–110%) after 0, 3 and 6 months storage at 40 °C/75% RH. After 6 months at accelerated ICH stability conditions, the tablets showed less than 5% loss in assay value from initial value. Levothyroxine sodium pentahydrate tablets manufactured with dibasic calcium

Table 3
Effect of pH modifying additives on the stability (% recovery) of levothyroxine tablets stored for 6 months at 40 °C/75% RH

pH modifier	Months		
	0	3	6
Without pH modifier[b]	101.58 (0.76)[a]	91.10 (0.62)[a]	87.19 (0.37)[a]
Sodium carbonate[b]	96.57 (2.41)[a]	98.77 (4.45)[a]	95.21 (3.55)[a]
Sodium bicarbonate[b]	96.02 (2.75)[a]	95.12 (2.88)[a]	94.67 (2.28)[a]
Magnesium oxide[b]	99.98 (1.08)[a]	98.65 (0.93)[a]	96.84 (0.76)[a]
Tartaric acid[b]	100.21 (0.79)[a]	83.36 (1.36)[a]	78.27 (0.63)[a]
Citric acid[b]	100.51 (0.71)[a]	87.56 (1.64)[a]	74.35 (0.901)[a]

[a] Percent recovery of levothyroxine/(% moisture).
[b] Each 100 mg tablet containing 50 μg levothyroxine sodium pentahydrate 10% above-mentioned pH modifier, and 88.9% dibasic calcium phosphate.

phosphate and acidic additives, namely tartaric acid and citric acid did not meet USP assay requirements after only 3 months at 40 °C/75% RH. Levothyroxine sodium pentahydrate tablets manufactured with dibasic calcium phosphate and no pH modifier assayed 91.1% after 3 months and met USP assay requirements. However, the same tablets assayed 87.2% after 6 months, and thus, they did not meet USP assay requirements at the extended time (Table 3). The results indicated that by adding basic pH modifiers the stability of levothyroxine sodium pentahydrate tablets with dibasic calcium phosphate was improved. In contrast, the use of acidic pH modifiers (negative control), enhanced degradation.

It was concluded that the use of basic pH modifiers is a potential technique for improving the stability of levothyroxine sodium pentahydrate tablets.

As discussed earlier, the inherent pH of the microenvironment found in the compressed tablets did not coincide with the pH of maximum stability of levothyroxine sodium pentahydrate. Thus when basic pH modifiers were employed to adjust the microenvironment of tablets, greater drug stability was observed.

4. Conclusions

Levothyroxine sodium pentahydrate drug substance was stable at accelerated ICH stability conditions for 6 months and was non-hygroscopic in normal processing conditions.

The degradation of levothyroxine sodium pentahydrate tablets was influenced by the type of excipients used in the formulation. Tablets made with some of the most commonly used diluents, anhydrous lactose, starch, and microcrystalline cellulose, showed a significantly greater loss in potency after 6 months at 40 °C/75% RH than tablets made with mannitol or dibasic calcium phosphate. The ∼30% loss in potency was accompanied by significant moisture gain (lactose, 0.8–5%; and starch, 7.8–10.25%), or associated with an inherently high moisture content initially (microcrystalline cellulose, 6.2%). Under the same conditions, tablets made with mannitol or dibasic calcium phosphate showed only a ∼15% loss in potency, and, these tablets contained less than 1% moisture initially and after 6 months.

While moisture control improved stability, it was not enough to stabilize the formulation to meet ICH stability criteria. This was demonstrated in tablets containing 88.9% dibasic calcium phosphate and 10% of an acidic pH modifier (citric or tartaric acid). These tablets had less than 1% moisture, yet loss in potency was ∼25% after 6 months at 40 °C/75% RH. However, tablets made with 88.9% bibasic calcium phosphate and 10% of a basic pH modifier (sodium carbonate, sodium bicarbonate, or magnesium oxide) met the ICH stability criteria for potency for 6 months at 40 °C/75% RH.

From the present research, it was concluded that levothyroxine sodium pentahydrate stability in tablets is best in the presence of a diluent with low moisture content and uptake, such as dibasic calcium phosphate, and a basic modifier. Results obtained with pH-adjusted aqueous slurries suggest that it may be possible to obtain stable formulations with other excipients, such as mannitol, as long as a pH modifier is included.

The degradation pathways observed were deiodination, deamination and decarboxylation. In the presence of basic additives, levothyroxine sodium pentahydrate showed reduced degradation both in a stressed environment, slurries at 50 °C for 1 month, and in tablets at accelerated ICH stability conditions for 6 months.

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