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Stability of levothyroxine tablets in blister packaging versus bottles and vials under simulated in-use conditions

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Abstract

Introduction: Levothyroxine, the standard-of-care treatment for hypothyroidism, is susceptible to degradation when exposed to light and moisture and is an FDA-designated narrow therapeutic index drug. In this report, we examined how different packaging (e.g., cold form blister packs, manufacturer's bottles, or pharmacy amber vials) affects the physicochemical integrity and potency of levothyroxine in conditions simulating real-world patient use.

Methods: In part 1 of this study, we evaluated changes in the physicochemical properties (e.g., moisture gain, hardness, and disintegration time) of levothyroxine tablets stored in high-density polyethylene (HDPE) bottles, amber vials, and blister packs when exposed intermittently to different relative humidities (RH), 25 °C/75% RH and 25 °C/90% RH for 90 days, or 54 °C/75% RH continuously for 2 days. In part 2 of the study, we compared the potency of levothyroxine tablets in bottles and aluminum/aluminum cold form blister packs exposed to 28 °C/65% RH intermittently over 105 days and continuously over 30 days.

Results: Moisture content, hardness, and disintegration time were relatively unchanged for blister-packaged levothyroxine tablets under all conditions studied. Conversely, the physicochemical properties of tablets stored in amber vials and bottles were altered over time. Levothyroxine potency remained relatively consistent for blister-packaged tablets (100.8% at baseline, 99.6% at day 105) and decreased for bottled levothyroxine (101.4% at baseline to 93.9% at day 105).

Conclusion: Levothyroxine packaging can influence tablet integrity. Blister packages preserved physicochemical properties and potency better than bulk bottles. Additional studies are needed to determine the impact of packaging and changes in tablet integrity on patient outcomes.

Keywords: Levothyroxine, Blister packaging, Stability, Humidity, Potency

Introduction

Hypothyroidism affects almost 5% of the United States' population (Institute and of Diabetes and Digestive and Kidney Diseases. 2021). Levothyroxine has been the standard-of-care treatment for hypothyroidism for approximately 60 years and is currently one of the most prescribed drugs in the USA (Chiovato et al. 2019; ClinCalc 2021). The United States Food and Drug Administration (FDA) has designated levothyroxine as a narrow therapeutic index (NTI) drug, requiring that formulations maintain between 95 and 105% potency throughout the duration of their shelf life to achieve therapeutic efficacy and avoid serious side effects (United States Food and Drug Administration. n.d.; Gottwald-Hostalek et al. 2017). As such, measures to ensure drug stability and maintain potency are imperative.

Levothyroxine is known to be highly sensitive to light and moisture and should ideally be stored in a low

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relative humidity environment at 20–25 °C (Garber et al. 2012; Collier et al. 2010; Benvenga et al. 2017). However, exposure conditions in home environments and/or during mail delivery can be difficult to control and may lead to imperfect storage. Indeed, improper storage of levothyroxine has been linked to refractory hypothyroidism, indicating that suboptimal storage conditions may result in decreased potency and poorer patient outcomes (Benvenga et al. 2017).

Proper packaging is important for preserving the physical and chemical properties of drugs by providing protection against external elements that can alter the parameters of the product, such as moisture, light, and oxygen (Healthcare Compliance Packaging Council. n.d.). Drug packaging should also support effective use of the medication by the patient within their daily lifestyle to maintain drug potency during real-world use conditions. The Healthcare Compliance Packaging Council recently reported that unit-dose high barrier blister packaging is better protected against degradation of three common prescriptions (lisinopril, metformin, and simvastatin) during normal daily use than manufacturer's bottles and polypropylene amber pharmacy vials (Healthcare Compliance Packaging Council. n.d.).

At present, levothyroxine is available in the USA in a variety of packaging, with the majority of prescriptions dispensed in bottles and amber vials versus unit-dose cold form blister packs. The objective of this study was to compare the physicochemical properties and chemical stability of levothyroxine tablets when packaged in blister packs versus bottles and amber vials in environments that simulate real-world use.

Methods

We performed a two-part study to evaluate the physicochemical properties and chemical stability of levothyroxine tablets dispensed in different types of packaging. Normal laboratory safety procedures were followed when handling levothyroxine (e.g., gloves, lab coats, etc.), and small samples were prepared in a well-ventilated lab or in a fume hood.

For the first part of the study, we evaluated physical changes to the tablets such as moisture gain, hardness, and disintegration time of levothyroxine tablets when stored in bottles, amber vials, or blister packs under 3 different environmental conditions. Two of the conditions were designed to simulate at-home storage and administration by patients/consumers (patient-use conditions) over 90 days, and one was representative of mail-order shipping conditions over 2 days. In the second part of the study, we assayed potency of levothyroxine tablets stored in bottles versus blister packs under 2 patient-use conditions: intermittent environmental exposure for 105 days and continuous exposure for 30 days.

Part 1

Study materials

For the first part of the study, samples consisted of 100 µg levothyroxine tablets in aluminum/aluminum cold form blister packs (Euthyrox®, Provell Pharmaceuticals, LLC), 100 µg levothyroxine tablets of another major brand marketed in the USA in 90-count (ct) manufacturer's high-density polyethylene (HDPE) bottles, and 100 µg levothyroxine tablets in 90-ct amber pharmacy vials that were dispensed from 1000-ct HDPE bottles. All samples were delivered in their original/sealed packaging and stored unopened at room temperature until the beginning of the study.

Study design

The 3 sample types (blister pack, 90-ct bottle, and dispensed amber vials) were incubated for 90 days in environmental chambers (Caron Products, Marietta, Ohio) calibrated to maintain two relative humidity (RH) environments: 25 °C/75% RH and 25 °C/90% RH, respectively. Cotton was removed from the bottles upon opening to investigate exposure to humidity without the interference of cotton or desiccant, as patients often remove these items. In addition, a separate set of samples were exposed continuously to a 54 °C/75% RH environment for 2 days to simulate high-temperature exposure during shipping. To mimic an actual patient's usage in taking medications each day, the bottles and amber vials were opened once every weekday (excluding holidays) and kept open at the designated exposure condition for no more than 1 min to expose the product to moisture. When monitoring moisture gain, one tablet from the vial and bottle containers was also removed each day to simulate the changing headspace in the containers as the product was used. Because they were sealed, blister-packaged tablets were not removed and discarded each day. Tablets were removed from blister packs on testing days only. The 25 °C/75% RH and 25 °C/90% RH patient-use samples were tested at day 0 (prior to incubation) and after incubation for 10, 20, 30, 45, 60, and 90 days for hardness and disintegration time. For moisture gain, tablets were tested on day 0 and at more frequent intervals over the course of 90 days. The shipping condition samples were tested on days 0 and 2 for these same parameters. Separate sets of bottles, amber vials, and blister packs were used for each test condition and each physicochemical property assessed.

Study assessments

Moisture gain was measured gravimetrically on an analytical balance (Adam Equipment Inc., Oxford, Connecticut). Any weight increase was attributed to moisture gain. Baseline tablet-to-tablet weight variation was determined by measuring the weight of 10 tablets from each manufacturer and calculating both the average weight, standard deviation (SD), and weight relative SD. Levothyroxine bottles and amber vials were weighed immediately after receipt and placed into their respective environments. One tablet was removed per business day from each bottle and vial. At each testing interval, bottles and amber vials were weighed, and a weight per tablet was calculated based on the total package weight and the number of tablets present in the package. This weight per tablet was compared to the average tablet weight previously determined for each sample. To avoid any potential error caused by weight loss from torn packaging, blister packs were tested differently. Blister packs with all doses removed (i.e., empty) were weighed before exposure and at the standard test intervals. Multiple empty blister packs were weighed and results averaged. At each test interval, any weight gain of the empty blister pack was subtracted from the weight gain of the test blister pack to correct for any changes in measurement (e.g., balance stability).

Tablet hardness was tested using a calibrated tablet hardness tester (Key International Inc., Cranbury, NJ, USA). The test method conformed with standard United States Pharmacopeia (USP) testing (United States Pharmacopeia. General Chapter,⟨1217⟩Tablet breaking force. n.d.). Tablets were tested in triplicate, and the data were averaged. Tablet-to-tablet hardness variation was determined by measuring the hardness of 20 different tablets from the same product and determining average hardness, SD, and relative SD. At each test interval, tablet hardness, SD, and relative SD were calculated and compared to the baseline hardness values.

Disintegration time was measured at an independent laboratory via a calibrated disintegration tester (Vanguard Pharmaceutical Machinery Inc., Texas) by submerging tablets in an aqueous medium at 37.8 °C. Testing was done in duplicate at two different laboratories. To determine variation in disintegration time, testing was repeated 5 times using different tablets of the same product to find a disintegration time average, SD, and relative SD.

Part 2

Study materials

In the second part of our study, we tested the chemical stability and potency of aluminum/aluminum cold form blister-packaged 100 µg levothyroxine tablets (Euthyrox®, Provell Pharmaceuticals, LLC) and 90-ct HDPE-bottled 100 µg levothyroxine tablets of the other major brand marketed in the USA in environmental conditions approximating patient/consumer use. Two sets of samples were obtained for each product, and all samples were stored in their original packaging at room temperature until the beginning of the study.

Study design

Bottled and blister-packaged levothyroxine tablets were incubated in an environmental chamber (Memmert HPP110 Chamber, Memmert, USA, LLC) at 28 °C/65% RH for 105 days. Cotton and desiccant were removed from bottles before incubation. To simulate patient-use conditions, the lid was removed from the bottle for approximately 1 min on each weekday (excluding holidays), and a tablet was removed. Boxes containing the blister packs were also exposed to the chamber atmosphere by opening the end of the box for the same 1-min exposure, but the blister inserts were neither removed from the box nor opened. Bottled samples were assayed for levothyroxine potency prior to incubation (day 0) and after incubation for 14, 32, 46, 75, 90, and 105 days (Supplemental Table 1). Based on preliminary data, which suggested good potency stability for blister-packaged tablets, these samples were assayed only on days 0, 32, 75, and 105. Duplicate confirmation testing was performed at a second independent laboratory (Primera Analytical Solutions Corp.) on days 0, 32, and 105.

After the study had begun, it was noted that leaving the bottles open for 1 min in the chamber was insufficient for the humidity to return to 65% RH, as humidity was lost each time the chamber door was opened. As a result, the protocol was modified to leave the bottles open until the chamber RH recovered to the target level. This resulted in the bottles being open in the chamber for approximately 8 min for the remainder of the study days. Because of the observation that the tablets may not have been exposed to the desired humidity level in the initial stages of the experiment, an additional bottle of tablets was added to the study for continuous exposure to the chamber atmosphere (28 °C/65% RH). The bottle was prepared by removing the cotton and desiccant and replacing the cap with a covering of filter paper (Whatman cellulose) to allow the tablets to equilibrate to the target RH without collecting moisture. This additional sample was incubated over 30 days starting on day 75 of the original study schedule. It was tested on study days 75, 90, and 105.

Study assessments

The current USP monograph procedure requires no fewer than 20 tablets to be ground by hand to prepare

a composite test sample, and then a calculated weight of sample, containing approximately 100 µg of active pharmaceutical ingredient (API, levothyroxine sodium), should be used (United States Pharmacopeia. Levothyroxine sodium tablets. n.d.). Therefore, for preparation of samples for each assay, 20 tablets were removed from the blister packaging or bottle and manually ground to a fine powder in a clean, agate mortar to create a composite test sample containing 100 µg API. During some initial work and during this study, some variability was noted in the assays, which were due to differences in grinding. When more care was taken to produce uniform, ground material, the assay results were more consistent.

The prepared solution was analyzed on a Shimadzu LC2020CHT high-performance liquid chromatography (HPLC) system equipped with a UV detector set at 225 nm. The sample separation was performed with a Microsorb-MV 100–5 CN column using a 35:65 acetonitrile:water mobile phase. For the assay of levothyroxine, the Alliance method produced similar results to the manufacturer method which utilized a gradient separation on ultra-performance liquid chromatography (UPLC). As this study was concerned with tracking the stability of levothyroxine (T4), the Alliance method was suitable for determination of this component while not being a truly stability-indicating method.

Composite test samples were prepared and analyzed in duplicate, and results were averaged. On days when testing was also performed at the Primera Analytical Solutions Corp., results from the duplicate composite samples from both laboratories (4 total samples) were averaged. Both laboratories used the validated USP 41 monograph HPLC analytical method and the same HPLC column for analysis to minimize differences due to instrumentation. Samples were run at two different laboratories to allow for multiple determinations of the same samples to ensure the HPLC methodology reliably detected levothyroxine over the course of the study.

Despite using a validated levothyroxine assay with good precision, more variability was observed in tablets from bottles than blister-packaged tablets. Therefore, over the course of the study, some of the results were investigated and rerun to improve the assay. These investigations indicated that the sample preparation steps for extraction of drug substance that provided acceptable results for blistered tablets had to be modified slightly to produce more consistent assay values for the bottled tablets. The HPLC settings and procedures remained the same, but the sample extraction methodology was modified over time to produce more reliable results due to differences in tablet composition or manufacturing of the tablets. The primary changes were related to improving the manual grinding of the tablets to produce more uniform sample powder and improving the cleaning of the mortar and pestle to avoid carryover or cross contamination of samples. Because the original method was optimized for Euthyrox only, these sample preparation issues were only observed once the study began using bottled tablets. A revision history of the assay method is shown in the supplemental materials (Supplemental Table 2).

Results

Part 1: Physicochemical properties

The average baseline weight of blister-packaged levothyroxine tablets was 99.1 mg (*SD* 0.92 mg; weight relative *SD* 0.928%). Levothyroxine tablets packaged in bottles and amber vials had a baseline average weight of 131.4 mg (*SD* 1.15 mg; weight relative *SD* 0.875%). Under both 25 °C/75% RH and 25 °C/90% RH patient-use conditions, blister-packaged levothyroxine tablets absorbed little to no moisture over time (0.026% weight gain at 90 days for both 25 °C/75% RH and 25 °C/90% RH) (Fig. 1 A and B). Conversely, moisture absorption increased over the 90-day study period in bottled levothyroxine tablets. Moisture gain was approximately twice as much at 90 days under 25 °C/90% RH conditions (1.037% weight gain) than under 25 °C/75% RH (0.478% weight gain). The sharpest increase in moisture gain was seen in the first 10 days (0.379% at 25 °C/75% RH, 0.683% at 25 °C/90% RH). Levothyroxine tablets stored in amber vials also demonstrated moisture gain over time, although to a lesser extent than bottled levothyroxine tablets (0.169% weight gain at 90 days, 25 °C/75% RH; 0.300% weight gain at 90 days, 25 °C/90% RH). When exposed continuously for 2 days to extreme shipping conditions (54 °C/75% RH), moisture increased in levothyroxine tablets stored in bottles (2.240% weight gain at day 2) and amber vial products (2.051% weight gain at day 2), but not blister-packaged levothyroxine tablets (0.003% weight gain at day 2) (Fig. 1C).

The average baseline hardness of blister-packaged levothyroxine tablets was 45.2 Newtons (N) (*SD* 2.79 N; hardness relative *SD* 6.17%). Bottled and vialed tablets had an average baseline hardness of 42.8 N (*SD* 1.10 N; hardness relative *SD* 2.57%). Under both 25 °C/75% RH and 25 °C/90% RH patient-use conditions, blister-packaged levothyroxine tablets underwent very little change over time (4.43% change at 90 days, 25 °C/75% RH; 8.19% change at 90 days, 25 °C/90% RH) (Fig. 2 A and B). Conversely, hardness decreased substantially over the 90-day study period in bottled levothyroxine tablets, with an approximately 4 times greater decrease in hardness under 25 °C/90% RH versus 25 °C/75% RH conditions (−37.66% change at 90 days, 25 °C/90% RH; −10.00% change at 90 days, 25 °C/75% RH). Levothyroxine tablets stored in amber vials had a variable hardness change over

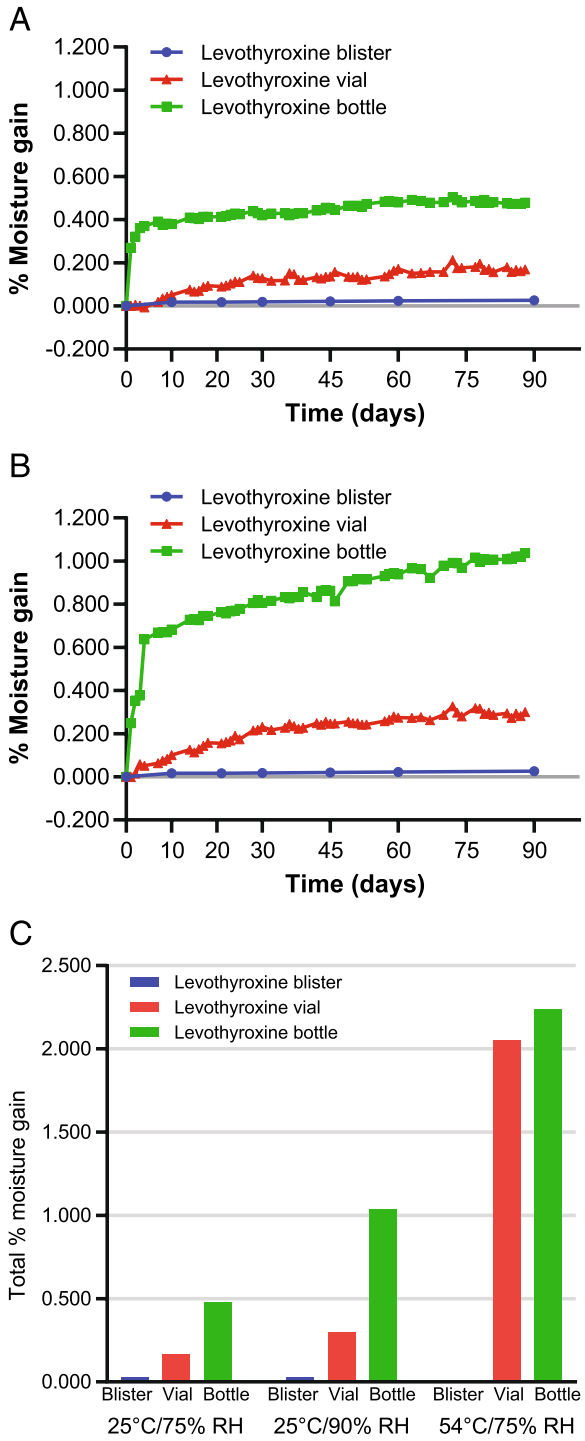

Fig. 1 Moisture gain of levothyroxine tablets. **A** Percent moisture gain over time: 25 °C/75% RH. **B** Percent moisture gain over time: 25 °C/90% RH. **C** Total percent moisture gain under 90-day patient use or 2-day shipping conditions. Abbreviation: RH, Relative humidity

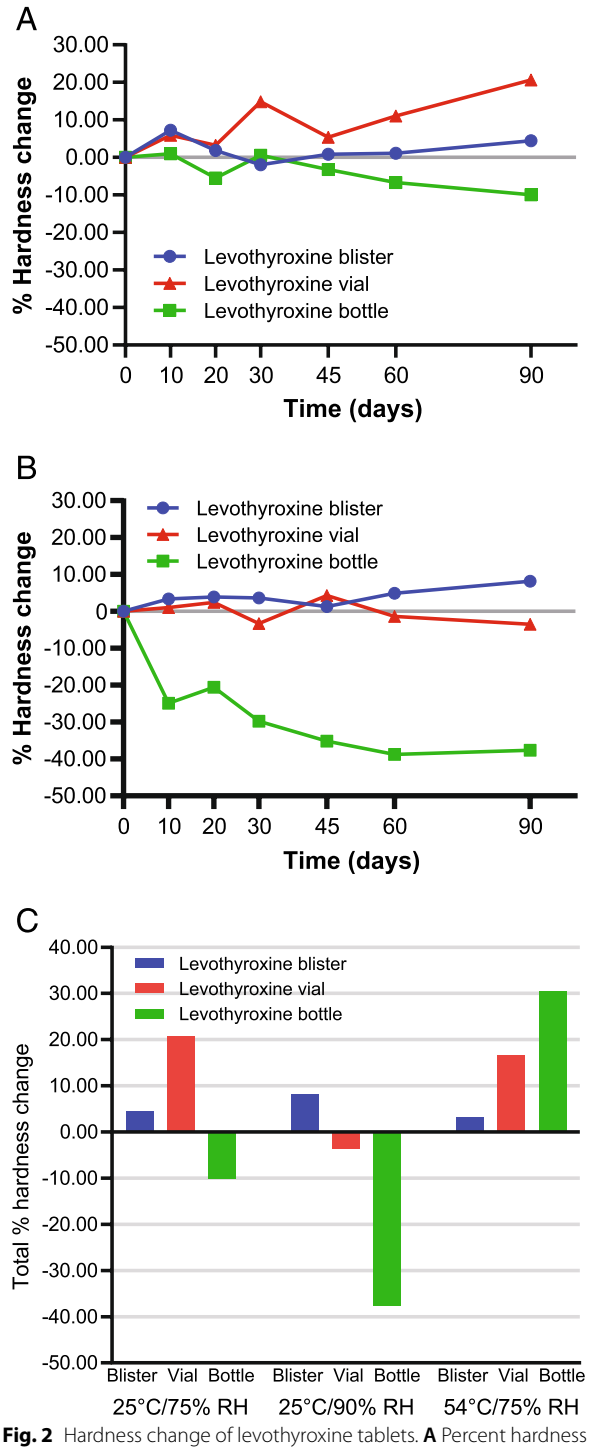

Fig. 2 Hardness change of levothyroxine tablets. **A** Percent hardness change over time: 25 °C/75% RH. **B** Percent hardness change over time: 25 °C/90% RH. **C** Total percent hardness change under 90-day patient use or 2-day shipping conditions. Abbreviation: RH, relative humidity

90 days, with hardness increasing at 25 °C/75% RH but decreasing at 25 °C/90% RH (20.62% change at 90 days, 25 C/75% RH; −3.53% change at 90 days, 25 °C/90% RH). When exposed continuously for 2 days to extreme shipping conditions (54 °C/75% RH), hardness increased in levothyroxine tablets stored in bottles (30.36% change at day 2) and amber vial products (16.57% change at day 2) (Fig. 2C). Blister-packaged levothyroxine tablets underwent a slight hardness increase (3.10% change at day 2).

The average baseline disintegration time of blister-packaged tablets was 243.6 s (*SD* 0.89 s; disintegration time relative *SD* 0.366%). Bottled and vialed tablets had a baseline disintegration time of 265.4 s (*SD* 3.53 s; disintegration time relative *SD* 1.33%). Under both 25 °C/75% RH and 25 °C/90% RH patient-use conditions, there was little change in disintegration time for blister-packaged levothyroxine tablets (−4.32% change at 90 days, 25 °C/75% RH; −5.35% change at 90 days, 25 °C/90% RH) (Fig. 3 A and B). Disintegration time increased 45.20% over the 90-day study period in bottled levothyroxine tablets at 25 °C/75% RH, with a similar change seen at 25 °C/90% RH (58.19% change). Levothyroxine tablets stored in amber vials also demonstrated an increase in disintegration over time (42.37% change at 90 days, 25 °C/75% RH; 38.98% change at 90 days, 25 °C/90% RH). When exposed continuously for 2 days to extreme shipping conditions (54 °C/75% RH), disintegration time increased in levothyroxine tablets stored in bottles (82.11% change at day 2) and amber vial products (34.46% change at day 2), compared to blister-packaged levothyroxine tablets (1.24% change) (Fig. 3C).

Part 2: Levothyroxine potency assay

Blister packs preserved levothyroxine potency consistently throughout the study (Fig. 4). The average levothyroxine content at baseline was 100.8% of the stated strength. On days 32, 75, and 105, the average potencies were 100.1%, 102.1%, and 99.6%, respectively, demonstrating that blister-packaged tablets remained within USP specifications for the duration of testing and showed low variability between samples (Supplemental Table 3) (Gottwald-Hostalek et al. 2017). In contrast, bottled levothyroxine showed a measurable decrease in levothyroxine potency over 105 days. At baseline, the average levothyroxine content was 101.4% of the stated strength. Values for 14 through 90 days ranged from 96.9 to 97.7%, and, at 105 days, the potency was 93.9%, which was outside of the USP specifications for this drug product.

Bottled tablets in the 30-day full exposure experiment showed an observable decline in potency (Fig. 5). Bottled tablets had 103.0% average levothyroxine potency at baseline; however, potency fell to 98.4% after 15 days and to 94.5% at 30 days (Supplemental Table 4). To

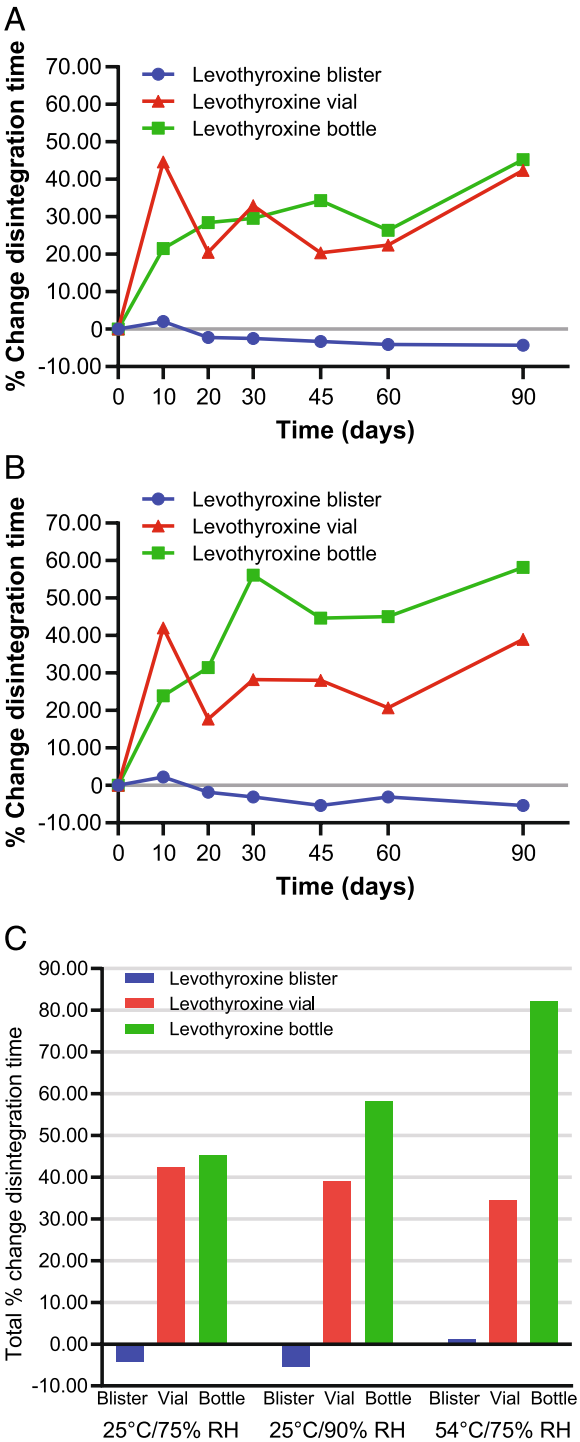

Fig. 3 Change in disintegration time of levothyroxine tablets. **A** Percent change in disintegration time: 25 °C/75% RH. **B** Percent change in disintegration time: 25 °C/90% RH. **C** Total percent change in disintegration time under 90-day patient use or 2-day shipping conditions. Abbreviation: RH, relative humidity

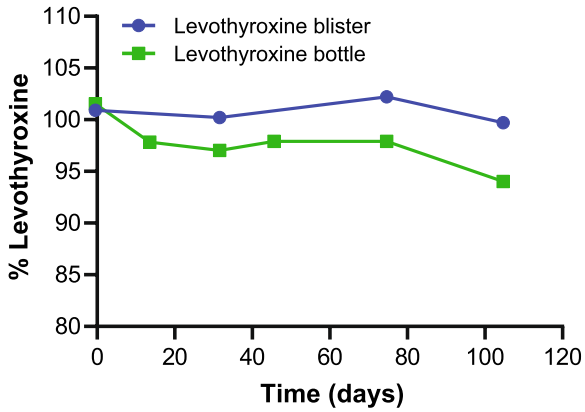

Fig. 4 Potency of levothyroxine tablets in blister packs and bottles over time

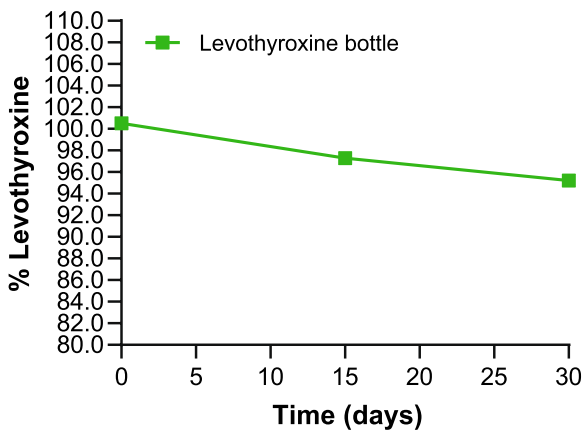

Fig. 5 Potency of levothyroxine during 30-day 28 °C/65% RH: full exposure study. Abbreviation: RH, relative humidity

understand product degradation under full exposure to high humidity, only the bottled product was investigated, and blister-packaged tablets were not included in the 30-day full exposure experiment as they could not be exposed continuously.

Although a validated assay was used for this study, there was some variability within duplicates and between labs. This observation was not unexpected as interlaboratory error can be significant even for validated methods. In this case, the average error was low and, estimated from replicate determinations of prepared standards, found to be approximately 0.8%–1.7% of the measured value.

Discussion

To our knowledge, this is the first study to evaluate the physicochemical integrity and potency of levothyroxine tablets when packaged in blister packs versus bottles or amber vials in environments that simulate real-world use. Blister packages allow for unit dosing to ensure that each individual tablet is protected from light, air, and moisture. It is therefore not surprising that the potency of blister-packaged levothyroxine tablets was maintained, and that moisture content, hardness, and disintegration time were relatively unchanged under all conditions studied.

In contrast, exposure to humidity resulted in an apparent increase in moisture content of the tablets (a key cause of product degradation) and an increase in disintegration time (an indicator of drug release properties and absorption rate) for both bottled and amber vial-packaged levothyroxine tablets under conditions designed to simulate patient use and mail-order shipping conditions. Tablet hardness was also impacted for levothyroxine tablets stored in bottles and amber vials, including both increases and decreases in hardness observed. We hypothesized that initial moisture absorption can cause an increase in a product's hardness due to the caking effect of the ingredient. However, as moisture levels increase further, the tablet softens, reducing hardness. Both changes to hardness are detrimental to the product because they impact the proper dissolution of the product and may affect the dosage a patient receives. Our findings are consistent with those of the Healthcare Compliance Packaging Council, where simvastatin, lisinopril, and metformin tablets showed more variable moisture content and hardness over time when stored in bottles and amber vials compared with blister-packaged samples (Healthcare Compliance Packaging Council. n.d.).

In part 2 of our study, a decrease in potency was observed for levothyroxine packaged in bottles. While the potency of bottled levothyroxine tablets was maintained at or above 95% for the 90-day in-use period, there was an ongoing decline. With continued exposure to humidity, day 105 levothyroxine levels decreased more than 5 percentage points, ultimately falling outside the USP acceptable range. In the 30-day exposure study, the levothyroxine potency of bottled tablets decreased steadily and dropped nearly 10 percentage points by day 30, again falling below USP. These findings demonstrate that bottled tablets can fall below USP potency within their expiration date if stored at suboptimal conditions. This is important because real-world shipping and end-consumer environments can be less predictable than our test conditions. For example, our results indicated that potency loss observed in bottled products would be greater when levothyroxine is stored in places of higher humidity, such as a bathroom, which is a common location for patients to store their medication. In addition, in some cases, levothyroxine tablets are initially packaged

and delivered to pharmacies as 1000-ct bottles, which are subsequently opened and redistributed into smaller samples for patient use. It is possible that the opening of bottles prior to dispensing could initiate moisture ingress and tablet degradation prior to the product being received by the patient. Other studies have shown that stability of levothyroxine is impacted by repackaging (Robertson and Glass 2019) and exposure to light (Mohamed and Abdallah 2016).

In contrast to European countries, where levothyroxine is generally dispensed in blister packs, most levothyroxine prescriptions in the USA are dispensed in amber vials or bottles. Our results show that blister packaging affords better protection of tablets and preserves product stability. Clinical studies are needed to evaluate the impact of tablet packaging and tablet integrity on patient outcomes.

Excipients have been shown to impact levothyroxine stability (Collier et al. 2010; Ledeți et al. 2020; Patel et al. 2003), and differences in tablets from different manufacturers beyond packaging (e.g., size, geometry, surface area, coated or not coated) could also potentially impact physicochemical properties and stability. However, these were not considered in this study as the goal was to assess stability of levothyroxine in the forms and packaging currently available to patients. In addition, impurities from degradation can contribute to possible toxicity. While impurities are an important consideration, the objective of this study was to examine changes to the drug tablet physical properties and the apparent (USP) assay value over time under various humidity conditions. Changes in assay were expected to be a more significant problem to a patient rather than toxicity due to impurities especially because levothyroxine is an NTI drug.

Limitations of this study included an unexpectedly high level of variability in levothyroxine potency within duplicates of bottled tablets with the initial testing protocol. This was likely due to sample preparation, large tablet size, and formulations from different manufacturers. Based on observations collected during the course of the study, the testing protocol was adjusted to produce more consistent results.

Conclusions

Our findings show that product packaging influences vulnerability of levothyroxine to degradation in conditions designed to simulate both shipping and everyday patient/consumer use. Real-world conditions may be even more variable than the conditions studied here, highlighting the need for measures to ensure levothyroxine stability and potency once it departs the manufacturing facility. Blister packaging reliably preserves the physicochemical properties and potency of tablets in both 25 °C/75% RH and 25 °C/90% RH and extreme shipping conditions. Clinical studies are needed to determine the possible therapeutic impact of different packaging on patient outcomes.

Abbreviations

FDA: United States Food and Drug Administration; HDPE: High-density polyethylene; HPLC: High-performance liquid chromatography; N: Newton; NTI: Narrow therapeutic index; RH: Relative humidity; SD: Standard deviation; USP: United States Pharmacopeia.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41120-022-00062-5.

Additional file 1: Supplemental Table 1. Sampling Schedule for the In-Use Stability Study of Levothyroxine Potency. **Supplemental Table 2.** Revision History of Levothyroxine Assay. **Supplemental Table 3.** Percent Potency of Levothyroxine: In-Use Stability. **Supplemental Table 4.** Percent Potency of Bottled Levothyroxine: Full Exposure.

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Authors' contributions

JC contributed to the conception or design of the study, to the acquisition of the data, and to the data analysis or interpretation. JC provided critical review and final approval of the manuscript for publication and agrees to be responsible for the work. The author read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

J. Chun reports his institution, Alliance Technologies, and received research funding from Provell Pharmaceuticals, LLC to conduct product stability testing. Alliance Technologies is an independent contract testing laboratory, and all work conducted is sponsored by each client. Provell Pharmaceuticals, LLC, through packaging labs or suppliers or directly, contracted stability testing with Alliance Technologies. Conclusions and reported results are determined based on data collected by Alliance Technologies and its contractors or technical experts. Dr. Chun also reports funding from Liveo Research, which subcontracts laboratory testing beyond Liveo's capabilities, to his institution.

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