Stability of Levothyroxine Sodium Tablets Marketed in Sudan

ABSTRACT

Stability of medicinal products is the extent to which a product retains, within specified limits throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics that it possessed at the time of its manufacture. The aim of this study is to evaluate real-time stability and photo-stability of levothyroxine sodium tablets marketing in Sudan. Levothyroxine sodium tablets from different manufacturers were kept at control room temperature (23–25°C); all the samples were analysed every month using the British Pharmacopoeia (BP) HPLC method. All tablets were kept in a closed glass dish and exposed to direct sunlight for 10 days to evaluate photo-stability using BP and HPLC methods. The results revealed that thyroxine tablets had become out of specification (88.0, 87.0 and 87.0%) after 15, 20 and 19 months, respectively, from the date of manufacturing and lost more than 5% from initial concentration after 8–9 months; and lost about 40% of its potency after exposure to sunlight. The shelf life of levothyroxine sodium dosage form should be <2 years to ensure that the dosage form was containing the correct dose when dispensed for use. It is evident from the analysis, sunlight has measurable effect on the stability of levothyroxine sodium even in solid dosage forms.

INTRODUCTION

The World Health Organisation (WHO) has defined quality assurance as a wide-ranging concept covering all matters that either individually or collectively influence the quality of a product; the stability of product throughout distribution channels until it reaches the user is one of the quality parameters.

Stability of medicinal products

United State Pharmacopeia (USP) has defined the stability of medicinal products as the extent to which a product retains within specified limits and throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics that it possesses at the time of manufacture.

The stability of a product is related to its resistance to the various chemical, physical and microbiological reactions that may change the original properties of the preparation during transport, storage and use. Other criteria of stability are the effects of such changes on the fitness of the product for use as a medicine. The stability is often expressed in quantitative term as shelf life that is the time during which the medicinal product is predicted to remain fit for its intended use under specified storage conditions.

Shelf-life

Shelf-life of medicinal products kept in its closed container under specified conditions is commonly defined from the date of manufacture or preparation until the original potency or content of active constituent has been reduced by 10%. This time is known as the $t_{10\%}$ or $(t_{90\%})$. Although it is often convenient to express shelf-life solely in terms of the chemical stability of the active constituent, it is essential that the other desirable properties of the product are retained during storage.
**Factors affecting product stability**

Each ingredient, whether therapeutically active or pharmaceutically necessary, can affect the stability of drug substance and dosage forms. Factors affecting stability of medicinal products include:

**Environmental factors**

The primary environmental factors that can reduce stability include exposure to adverse temperature, light, humidity, oxygen and carbon dioxide.

**Dosage form factor**

In dosage forms, reactions usually cause drug instability and loss of active drug content, and they usually do not provide obvious visual or olfactory evidence of their occurrence.

**Chemistry of levothyroxine sodium**

Levothyroxine sodium (formerly called thyroxine sodium in United Kingdom) is a sodium (2S)-2-amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propionate (Fig. 1). Optical rotation of levothyroxine sodium ranges between +16 and +20°. Melting point for thyroxine sodium is 235–236°, with decomposition.

**Stability of levothyroxine sodium**

Thyroxine is stable in dry air, but unstable in the presence of light, heat and humidity. In some cases overseas, thyroxin tablets were found unstable even at room temperature, and storage temperatures of 8–15°C were required to maintain potency. In the USA, the food and drug administration has recognised the stability and potency problems with oral thyroxine.

The preparation could potentially have adverse effects on health. It is therefore very important that thyroxin tablets should be kept in their original container and stored in a cool dry place.

The expiry date for Australian manufacture thyroxin tablets is 1 year from the date of manufacture. There are 200 tablets in a bottle, so it is possible that tablets could expire before a course of treatment is completed. However, stock with shelf life of 18 months will soon be available; this formula requires refrigeration all time.

**Objectives**

Levothyroxine sodium has narrow therapeutic index. Therefore, it is particularly important that the available amount of the active drug should be consistent for a given strength in tablets; hence careful titration of dose is needed.

The objectives of this study are to:

1. Evaluate real time stability of levothyroxine sodium tablets.
2. Study photo-stability of levothyroxine sodium tablets.
3. Assess the quality of levothyroxine sodium tablets from different manufacturer marketing in Sudan.

**MATERIALS AND METHODS**

**Materials and equipments**

**Reference standard and chemicals**

- **Reference standard**
  - Levothyroxine sodium reference standard; batch no. A010445003, potency was 99.99%, manufactured by Acros Organic/Belgium.
  - Liothyronine standard; batch no. A010434001, potency was 99.95%, manufactured by Acros Organic/Belgium.

- **Chemicals**
  - Acetonitril, HPLC grade manufactured by Scharlau; Spain
  - Methanol analytical grade manufactured by Scharlau; Spain
  - Phosphoric acid BDH Laboratory England
  - Sodium hydroxide manufactured by Barcelona; Spain

**Equipment**

- Eknuer high performance liquid chromatography (HPLC): instrument equipped with pump K1001, UV detector 2600 and injection loop 20 µl and connected to software programmed as recorder.
- Ultra sonic bath

**Pharmaceutical preparations**

1. Thyrorin 100 µg (L-thyroxine sodium 100 µg, batch no. Ty 02, date of manufacture: 9/05, date of expiry: 9/08. Manufactured by Pharmedic Laboratories Ltd, Lahore, Pakistan).
2. Eltroxin 50 µg (L-thyroxine sodium 50 µg, batch no. 050897A, manufacture date: 3/05, expiry date: 3/07. Manufactured by GlaxoSmithKline, New Cairo, Egypt).
RESULTS

Calibrations curve

A calibration curve was constructed for levothyroxine sodium standard solution against the corresponding peak area. It gave linearity in the concentration range (10–100 µg/ml) with a regression of 0.999 (Table 1 and Fig. 2).

Results of analysis of pharmaceutical preparations

Assay and uniformity of content of levothyroxine sodium tablets

The three pharmaceutical preparations were assayed and their uniformity of content were tested using BP HPLC method; the assay was done three times in different days and the relative standard deviation of all the results were found <2%. The results obtained are shown in Table 2 and 3.

Photo-stability of levothyroxine sodium tablets

Levothyroxine sodium tablets kept in a closed glass dish that were exposed to direct sunlight for 10 days showed that there was a great effect of sun on the stability of levothyroxine even in solid dosage form; the results obtained by the HPLC method are given in Table 4.

Methods

Calibration curve

Concentrations of 10–100 µg/ml were obtained from freshly prepared solution (A) by serial dilutions using methanol:water (1:1) as solvent. Quantitative analysis of these solutions was carried out using the HPLC method, described before. Each sample was injected two times and their area under the peak corresponding to each injection of each concentration was obtained. This procedure was repeated three times.

Analysis of Levothyroxine sodium tablets

The assay and uniformity of content were carried out using HPLC method, described in the BP for the levothyroxine sodium tablets.

Study the stability of levothyroxine sodium tablets

Two types of stability studies were conducted on levothyroxine sodium tablets.

Photo-stability of levothyroxine sodium tablets: Photo-stability of levothyroxine sodium tablet was carried out using Eltroxin tablet of 100 µg (batch no. 071425A manufacturing date 4/07, expiry date 4/09). The tablets were kept in a closed glass dish and exposed to direct sunlight for 10 days. Then analysis was done as follows; 10 tablets were accurately weighed and crushed (using mortar and pestle). A weight of powder equivalent to about 100 µg of levothyroxine sodium was transferred quantitatively to 10 ml amber volumetric flask, dissolved in a solvent containing methanol and sodium hydroxide 0.1M (1:1) by the aid of ultrasonic and then shaked for 15 min. The volume was completed using the same solvent, as a control solution, a solution was prepared in the same manner using ten tablets from the same batch stored at room temperature; then analysis was done against levothyroxine sodium standard solution.

Real-time stability study of levothyroxine sodium tablets: Pharmaceutical preparations were kept at control room temperature (23–25°C) and a real-time stability study was done. The samples were analysed periodically using the BP HPLC method.

Table 1

<table>
<thead>
<tr>
<th>Area</th>
<th>Conc. (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>68.37</td>
<td>100</td>
</tr>
<tr>
<td>54.02</td>
<td>80</td>
</tr>
<tr>
<td>27.24</td>
<td>40</td>
</tr>
<tr>
<td>13.9</td>
<td>20</td>
</tr>
<tr>
<td>7.09</td>
<td>10</td>
</tr>
</tbody>
</table>
pink on exposure to light. Exposure of thyroxin in diluted aqueous solution to light energy, gamma radiation, causes deiodination and transformation into other iodinated organic molecules. Following the extraction of thyroxin from sodium (during stability indicating HPLC analysis), results indicated that 200 µg pink tablet from one manufacturer contained an excipient or excipients that accelerated degradation of thyroxin. This catalytic effect was suggested to require the presence of light.

**Real-time stability study of levothyroxine sodium tablets**

Pharmaceutical preparations were kept at control room temperature (23–25°C) and a real-time stability study was done. The samples were analysed periodically using the BP HPLC method. The study was not started at first month from the date of manufacture. The study was performed as follows:

- For Thyroidin 100 µg, studies were conducted on samples after 7 months from date of manufacture.
- For Eltroxin 50 µg, the studies were conducted on samples after 11 months from the date of manufacture.
- For Eltroxin 100 µg, the studies were conducted on samples after 10 months from the date of manufacture.

(Table 5)

From the above study, it is observed that Tyrosine 100 µg has become out of specification (88.0%) after 15 months from the date of manufacture and lost more than 5% from initial concentration after 8 months from initial concentration; which indicated instability according to WHO guidelines, while Eltroxin (50 and 100 µg) became out of specification (87.0%) after 20 and 19 months, respectively, from the date of manufacture and both lost more than 5% from initial concentration after 9 months; which reveals that 24 months is not suitable shelf life for levothyroxine sodium tablets in Sudan. These results confirm with the food and drug administration (FDA) announcement; that orally administered drug products containing levothyroxine sodium are new drugs and there is new information showing significant stability and potency problem with orally administered levothyroxine sodium products. These products fail to maintain potency through the expiration date (Fig. 3).

Orally administered levothyroxine sodium products, including the market leader, have reported recalls that are the result of potency or stability problems. Since 1991, there have been no <10 firm-initiated recalls of levothyroxine sodium tablets involving 150 lots and more than 100 million tablets. At one firm, potency problems with levothyroxine sodium tablets resulted in

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**Table 2** Linearity data for the levothyroxine sodium standard solution in methanolic sodium hydroxide by the HPLC method.

<table>
<thead>
<tr>
<th>Consistency of slope</th>
<th>0.677 ± 0.0045</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.239</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.999</td>
</tr>
<tr>
<td>Linearity range</td>
<td>10–100 µg/ml</td>
</tr>
</tbody>
</table>

**Table 3** Assay and uniformity of content of levothyroxine sodium tablets.

<table>
<thead>
<tr>
<th>Levothyroxine sodium tablets</th>
<th>Eltroxin 100 µg</th>
<th>Eltroxin 50 µg</th>
<th>Thyroidin 100 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniformity of content</td>
<td>90.2</td>
<td>91.5</td>
<td>91.8</td>
</tr>
<tr>
<td>Assay (%w/w)</td>
<td>93.3 ± 1.2</td>
<td>93.7 ± 0.88</td>
<td>94.1 ± 0.92</td>
</tr>
</tbody>
</table>

**Table 4** Results of sunlight effect on levothyroxine sodium tablets.

<table>
<thead>
<tr>
<th>% w/w Content at zero time ± SD</th>
<th>% w/w Content after 10 days of exposure to sunlight ± SD</th>
</tr>
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<tbody>
<tr>
<td>96.0 ± 0.91</td>
<td>56.9 ± 0.71</td>
</tr>
</tbody>
</table>

**Table 5** Results of real-time stability study of levothyroxine sodium tablets market in Sudan.

<table>
<thead>
<tr>
<th>Months</th>
<th>Content of thyroin¹ 100 µg (%w/w) ± SD</th>
<th>Content of eltroxin¹ 50 µg (%w/w) ± SD</th>
<th>Content of eltroxin¹ 100 µg (%w/w) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93.3 ± 1.2</td>
<td>93.7 ± 0.88</td>
<td>94.1 ± 0.92</td>
</tr>
<tr>
<td>2</td>
<td>92.8 ± 0.91</td>
<td>93.6 ± 0.89</td>
<td>93.6 ± 0.93</td>
</tr>
<tr>
<td>3</td>
<td>92.0 ± 0.61</td>
<td>93.3 ± 0.81</td>
<td>93.3 ± 0.79</td>
</tr>
<tr>
<td>4</td>
<td>91.7 ± 1.11</td>
<td>91.9 ± 1.31</td>
<td>92.1 ± 1.41</td>
</tr>
<tr>
<td>5</td>
<td>91.5 ± 0.81</td>
<td>91.9 ± 1.11</td>
<td>92.0 ± 1.31</td>
</tr>
<tr>
<td>6</td>
<td>91.0 ± 0.66</td>
<td>91.3 ± 0.82</td>
<td>92.0 ± 0.87</td>
</tr>
<tr>
<td>7</td>
<td>91.0 ± 1.19</td>
<td>91.0 ± 0.69</td>
<td>91.9 ± 0.95</td>
</tr>
<tr>
<td>8</td>
<td>90.8 ± 0.89</td>
<td>90.6 ± 1.28</td>
<td>91.8 ± 1.05</td>
</tr>
<tr>
<td>9</td>
<td>88.0 ± 0.78</td>
<td>90.0 ± 0.79</td>
<td>91.6 ± 0.59</td>
</tr>
<tr>
<td>10</td>
<td>85.7 ± 1.09</td>
<td>87.0 ± 1.21</td>
<td>87.0 ± 1.09</td>
</tr>
<tr>
<td>11</td>
<td>85.0 ± 0.68</td>
<td>86.0 ± 0.77</td>
<td>87.0 ± 0.81</td>
</tr>
</tbody>
</table>

**Fig. 3** Comparative graph of HPLC results of levothyroxine sodium tablets.
destruction of products and repeated recalls from 1990 to 1992. The firm destroyed 46 lots of levothyroxine sodium tablets that failed to meet potency or content uniformity specifications during finished product testing.

Between 1987 and 1994, FDA received 58 adverse drug experience reports associated with the potency of orally administered levothyroxine sodium products.

CONCLUSIONS

Unless the manufacturing process can be carefully and consistently controlled, orally administered levothyroxine sodium products may not be fully potent through the labeled expiration date, such variation in product potency presented actual safety and effectiveness concerns.

The shelf life of levothyroxine sodium dosage form should be <2 years to ensure that the dosage form was containing the correct dose when dispensed for use.

Levothyroxine sodium dosage form should not be supplied in large pack. As well, type of container should be considered to ensure protection from light.

Sunlight had measurable effect on the stability of levothyroxine sodium even in solid dosage forms.

REFERENCES