The Outcome of Formulation and Processing Variables on the Stability of Levothyroxine Sodium Tablets

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Abstract – Stability of formulations over shelf-life is critical for having a quality product. Choice of excipients, manufacturing process, storage conditions, and packaging can either mitigate or enhance the degradation of the active pharmaceutical ingredient [API], affecting potency and/or stability. The purpose was to investigate the influence of processing and formulation factors on stability of levothyroxine [API].

Keywords: Levothyroxine, Formulation, Sodium Pent Hydrate

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INTRODUCTION

Levothyroxine sodium pentahydrate is the sodium salt of the levo-isomer of thyroxine, an active physiological substance found in the thyroid gland. Synthetic version is primarily used in the treatment of hypothyroidism and as a thyroid stimulating hormone suppressant, in the treatment of various types of euthroid goiters [1]. Since its first inception in the market, there have been various recalls for these drug products from various manufacturers. The primary reason for these recalls is due to sub-potency before the expiration date of the drug product because of stability failures [2].

The use of thyroid extracts [containing the hormones levothyroxine and liothyronine] as a treatment for hypothyroidism, dates back to 1891. A more pure, synthetic form of levothyroxine was introduced in the 1950s. Despite experiments with liothyronine [T3], alone or in combination with levothyroxine [T4], the latter remains the dominant choice of clinicians and is the current standard thyroid hormone replacement in the UK for the treatment of hypothyroidism. Once diagnosed, patients normally start the estimated full or just below the full replacement dose immediately unless they are over 50, have severe hypothyroidism or have cardiac problems, in which case, the levothyroxine dose is gradually increased from an initial daily dose of 25 - 50 mcg levothyroxine. This is then increased by 25 – 50 mcg/day at 3-4 weekly intervals until a normal metabolic state is attained. Thyroid stimulating hormone [TSH] secreted by the anterior pituitary gland, plays a pivotal role in the control of the thyroid axis and serves as the most useful marker of thyroid status. Careful monitoring of serum levels of TSH is necessary until an appropriate dose of levothyroxine is reached. The treatment target is a TSH level within the normal range [0.4 - 4.5 mU/L]. TSH is monitored during chronic treatment, usually on an annual basis as chronic under-treatment or over-treatment may be associated with adverse symptoms and undesirable clinical outcomes.

Although expiration dating is based on the scientific data at normal and stressed conditions, not all the batches and strengths undergo stability testing and for this reason understanding the factors that affects the product stability is critical. Levothyroxine has been a subject of advisory committee meetings at FDA due to its potency and stability issues [3]. Levothyroxine has a complex stability profile and is sensitive to various environmental factors such as light, air, and humidity, among others [4–8]. Effects of some excipients have been studied by Patel et al. [8] and Gupta *et al*. [9]. However, in both the reports, the impurities remain largely unidentified. Thus stability of levothyroxine has not been systematically characterized in the presence of processing and formulation factors by a stability-indicating method which can identify majority of its degradation products.

REVIEW OF LITERATURE:

Stability of levothyroxine over its shelf-life and its clinical consequences In response to concerns expressed about

levothyroxine sodium products by health care professionals and patients that the potency of levothyroxine tablets may deteriorate prior to its expiry date, the FDA tightened the potency specifications for levothyroxine sodium from 90-110% to 95-105% in October 2007. It was hoped by this means to reduce the variability in the stability profiles between products that could have clinical consequences in achieving target thyroid hormone levels. In a similar move, the British Pharmacopoeia tightened the upper potency limit over shelf life from 110% to 105%, although the lower limit still remains at 90%.

Stability of Levothyroxine Sodium [13]

Stability of Pentahydrate Form:

The pure drug was weighed and placed in open amber glass containers to equilibrate with temperature and humidity conditions. The stability conditions were as follows: 25°C/0%RH and 40°C/0%RH [Fisher Scientific, St. Louis, MO, USA] and 25°C/60%RH and 40°C/75%RH [HotPak, Baltimore, MD, USA]. For conditions of 25°C/0%RH and 40°C/0%RH, the samples were placed in desiccators using indicating Drierite anhydrous calcium sulfate dessicants and positioned under the appropriate temperature condition. Humidity values were measured using a hygrometer [Fisher Sci, Suwanee, GA, USA].

To determine the chemical changes of levothyroxine sodium hydrate, the samples were analyzed at predetermined days [0, 3, 6, 10, 14, and 28]. Samples were weighed [10 mg] in three 100-mL amber glass volumetric flasks followed by the addition of 20 mL of sample diluent [10 mM NaOH–MeOH; 1:1 *v*/*v*], sonicated for 10 min, and filled to volume with sample diluent. One milliliter of each sample was then transferred to individual 10-mL amber volumetric flasks. One milliliter of theophylline internal standard [0.1 mg/mL] was then added and solution filled to volume with sample diluent. The contents of each solution were transferred to an automatic injector for HPLC analysis. The determination of the API was carried out by a previously determined validated method [10].

Stability of Dehydrated Form [13]

The API was weighed [50 mg] on a calibrated balance and placed in eight 1.5-mL amber glass septum vials for each stability condition [25°C/0%RH and 40°C/0%RH]. Samples were then placed in vacuum/gas compartments containing Fisher Scientific thermo-hygro readers [11-661-13, Suwanee, GA, USA] and color-indicating desiccants. A vacuum was used to remove the air from each compartment followed by a purge of nitrogen in each compartment. Compartments were then closed and placed in their temperature chambers, respectively.

Influence of Formulation Factors on Stability of Levothyroxine Sodium Pentahydrate [13]

Using accelerated conditions gives the opportunity to conduct stability studies in a shorter period of time. Commonly, conditions such as 40°C/75%RH are used as accelerated and last between 3 and 6 months. Increasing the temperature to 60°C places l-thyroxine in its threshold temperature which causes rapid degradation. Screening of excipients was performed at a higher temperature of 60°C as opposed to accelerated stability studies which are usually performed at 40°C for 6 months. The higher temperature would accelerate the degradation of levothyroxine as it was observed in another paper [5] that levothyroxine degrades rapidly at higher temperatures. Thus, a short term of 28 days was used in the paper in order to determine the excipients which caused instability of levothyroxine. The combination of drug and excipient in this temperature environment allows for expedited drug degradation studies. Moreover, the mechanism of degradation does not change at higher temperatures [5]. Another purpose of conducting this paper was to evaluate manufacturing conditions such as wet granulation followed by drying which is done at higher temperatures, although it did not last for more than a few hours. Thus, conducting a short-term stability paper at higher temperature would give an evidence of instability during manufacturing conditions [13].

Issues around bioequivalence of levothyroxine products: Currently licensed levothyroxine products in the UK were approved many years ago, under previous legislative requirements. Consequently, these products, which are used interchangeably, are not supported by clinical data such as bioequivalence as expected by today's standards. More recently, applications for marketing authorisations of new levothyroxine products have been supported by bioequivalence data comparing blood levels of levothyroxine for the intended new product with the brand leader. Lack of comparative bioavailability data aside, there are recognised issues with bioequivalence studies involving levothyroxine. Levothyroxine is not a drug as such but rather a natural hormone. Endogenous thyroxine is indistinguishable from exogenously administered levothyroxine, both in its biochemical characteristics and physiologic effects. Also, continued thyroidal secretion in paper models using healthy volunteers confounds pharmacokinetic data, such as the area under the concentration vs. time curve [AUC; a measure of how much drug has been absorbed] or the maximum plasma concentration [Cmax, a measure of the highest observed drug level in blood plasma]. These are

the typical parameters that are compared when establishing bioequivalence [interchangeablity] between drug products.

CONCLUSION:

Levothyroxine sodium pentahydrate drug substance was stable at long-term as well as accelerated stability conditions for the paper period of 28 days. It loses some of its moisture rapidly when placed in a dry environment; however, it is stable in the dehydrated form as well as seen from the studies conducted by placing a dried form under the stability conditions of 0% RH at 25°C and 40°C. Small changes in serum levothyroxine and triiodothyronine concentrations alter serum TSH. Individual response to slight changes in the amount of levothyroxine delivered to the body can be variable and there is literature evidence that in some patients, a small change in the amount of levothyroxine can alter their general sense of well-being and possibly lead to subclinical thyroid disease although this is not universally supported by experts.

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