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Comparative Assessment of the Physicochemical Properties of Different Brands of Levothyroxine

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Abstract: Levothyroxine is an oral form of drug that is used for hypothyroidism disorder. Hypothyroidism disorder is a condition in which the gland does not produce enough thyroid hormones for the body to perform its functions effectively. In the commercial market, various brands of levothyroxine are available that are frequently prescribed for hypothyroidism. In this study, we determined the comparative assessment of physicochemical properties of different brands of marketed available levothyroxine oral tablets in Karachi, Pakistan. In this study, we evaluated the pharmaceutical equivalency of different marketed brands of levothyroxine by using QC parameters, i.e., weight variation, thickness, hardness, and disintegration. Instruments used for different analyses included digital weighing balance, hardness apparatus, vernier caliper, and disintegration tester. Different brands of levothyroxine were purchased from the different community pharmacies for physicochemical analysis and performed physiochemical tests with the comparison of BP and USP specifications. The physicochemical properties of different marketed brands of levothyroxine were performed through digital weighing balance, hardness apparatus, vernier caliper, and disintegration tester. The weight variation is performed using digital weighing balance. First, we determined the parent drug, i.e., Synthroid .0833; however, the rest of the drugs including Eltroxin, thyroxin, and thyronorm are 0.170, 0.146, and 0.1043. The thickness was measured using vernier caliper, and the calculated values of Synthroid, Eltroxin, thyroxine, and thyronorm were 0.0640, 0.410, 0.0847, and 0.1106. The hardness was measured using hardness tester, and the calculated values for synthroid, Eltroxin, thyroxine, and thyronorm were 3.5400, 3.8300, 3.3700, 3.6800. The disintegration was measured with the disintegration tester, and the calculated values of Synthroid, Eltroxin, thyroxine, and thyronorm were 4 min;10 seconds, 1 min, 2 min; 48 seconds and 1 minutes; 43 seconds. Physicochemical properties of all four brands of levothyroxine showed slight differences within the range of BP and USP. This research compared the physicochemical properties of different marketed available brands of levothyroxine with those of a parent company in Karachi, Pakistan. Drug release investigation and bioequivalence should be performed in the near future for more authenticity and prescription confidence.

Keywords: levothyroxine, physicochemical properties, comparative study, weight variation, thickness, hardness, disintegration.

不同品牌左旋甲状腺素理化性质的比较评价

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摘要：左甲状腺素是一种口服药物，用于治疗甲状腺功能减退症。甲状腺功能减退症是一种腺体无法产生足够的甲状腺激素以使身体有效发挥其功能的疾病。在商业市场上，可以买到各种品牌的左旋甲状腺素，这些左旋甲状腺素经常被用于治疗甲状腺功能减退症。在这项研究中，我们确定了巴基斯坦卡拉奇市售的不同品牌左旋甲状腺素口服片剂的理化性质的比较评估。在本研究中，我们通过使用质量控制参数（即重量变化、厚度、硬度和崩解度）评估了不同市售品牌左甲状腺素的药物等效性。用于不同分析的仪器包括数字天平、硬度计、游标卡尺和崩解仪。从不同社区药房购买不同品牌的左旋甲状腺素进行理化分析，并进行理化测试，比较英国石油公司和美国药典规格。采用数显天平、硬度计、游标卡尺、崩解仪对不同市售品牌左甲状腺素的理化性质进行测定。重量变化是使用数字天平进行的。首先，我们确定了母体药物，即合成器.0833；然而，其余的药物包括艾曲辛、甲状腺素和甲状腺正常是 0.170、0.146 和 0.1043。使用游标卡尺测量厚度，合成器、艾曲辛、甲状腺素和甲状腺正常的计算值分别为 0.0640、0.410、0.0847 和 0.1106。使用硬度计测量硬度，合成器、艾曲辛、甲状腺素和甲状腺正常的计算值分别为 3.5400、3.8300、3.3700、3.6800。用崩解仪测定崩解度，合成器、艾曲辛、甲状腺素、甲状腺素的计算值为 4 分钟；10 秒、1 分钟、2 分钟；48 秒 1 分钟；43 秒。所有四个品牌的左甲状腺素的理化性质在英国石油公司和美国药典范围内均显示出细微的差异。本研究将不同市售品牌左甲状腺素的理化特性与巴基斯坦卡拉奇的母公司的理化特性进行了比较。应在不久的将来进行药物释放调查和生物等效性，以提高真实性和处方信心。

关键词：左甲状腺素，理化性质，比较研究，重量变化，厚度，硬度，崩解。

1. Introduction

Levothyroxine is an oral dosage form that is indicated for treating hypothyroidism and is also indicated for thyroidectomy patients and thyroid cancer patients [1]. L-Thyroxin is also known as Levothyroxine and is a synthesized form of the thyroid hormone thyroxin. The pure form of thyroxin was for the first time isolated from the thyroid gland of a dog by Edward Calvin Kendall at the mayo clinic. The hormone was prepared in 1927 by George Barger and Charles Robert Harington. Levothyroxine is a biochemically and chemically active synthetic t4 hormone. Indistinguishable physiologically from a natural one and it is administered when the natural hormone is defective in the body. The maximum effect comes in 4 to 6 weeks [2]. The artificial form of one of the body's natural thyroid hormones is levothyroxine (T4) thyroxine (T4) thyrotropin-releasing hormone (TRH) secreted by the hypothalamus, which then activates the anterior pituitary to secrete thyroid exciting hormone that consequently excites the thyroid to discharge eighty percent thyroxine, and twenty percent l-triiodothyronine thyroxine (T4) is converted by fifty percent to its active metabolites L-triiodothyronine (T3). The thyroid hormones then act by binding to proteins found within the cell nucleus of the thyroid receptor. Once within the nucleus, thyroid hormone acts to rise body breakdown during protein synthesis, usage of glycogen stocks, and other further tasks by directly inducing DNA transcription. Levothyroxine can mimic the body's endogenous T4 development by the thyroid circumstances where this mechanism is disrupted in a different type of hypothyroidism [3]. Levothyroxine was administered orally before meals, and levothyroxine required hospital monitoring. The adult dose of levothyroxine is 1.6 mcg/kg/day to 25 mcg/kg/day [4, 5]. Side effects include angina, increased heart rate, increased pulse rate, arrhythmias, myocardial infarction, breath shortness, nervousness, sickness, headache, sleeplessness, touchiness, skin outbreaks, hair loss, goiter, weight increase, and menstrual abnormalities. Prohibited levothyroxine in patients who have a deficiency of the adrenal hormone, increased heart rate patients, people who have high thyroid hormone, and myocardial infarction patients [4]. Different foods alter the absorption of levothyroxine [6, 7]. Papaya, soybean, grapefruit, and caffeine impact the absorption of levothyroxine [8–10].

2. Objective of the Study

The objective of this study was to compare

physicochemical properties of different brands of levothyroxine.

3. Materials and Methods

Instruments used for different analyses included digital weighing balance, hardness apparatus, vernier caliper, disintegration tester beaker, volumetric flask, pipette, and filter. Different brands of levothyroxine were purchased from the National Medical Centre pharmacy for physicochemical analysis. These brands include Thyroxine, Thyronorm, Synthroid, and Eltroxin. All these drugs have more than one year of expiry.

3.1. Weighing the Tablets

We took twenty tablets of each brand of levothyroxine brands, weighed each tablet separately by digital Ohaus weighing balance Model no. (B515825273), determined the weight of each tablet, and noted it.

3.2. Thickness of the Tablets

We took twenty tablets of each brand of levothyroxine, and the thickness of the tablets was identified using Thomas Scientific Vernier Caliper Model no. (1235C55). We determined the thickness of tablets by placing them one by one in a Vernier caliper and noting the thickness of each tablet in mm.

3.3. Hardness of the Tablets

We took twenty tablets from each brand of levothyroxine. The hardness of tablets was determined using the hardness tester MH Galvano scientific Model no (GH1). Hardness was checked by placing tablets one by one in the center of the hardness tester, then the hardness tester applied force from both sides. Continuation force was applied until the tablet broke. The time at which the tablet broke was noted. The hardness of the tablet was noted in newton.

3.4. Disintegration Time

We took one tablet from each brand and checked the disintegration time by using the disintegration apparatus, Galvano Scientific Model no. (121t). We placed six tubes and filled each tube with water and placed the tablet in it, then covered each tube with a small lid. Started disintegration apparatus and noted the time at which tablet spilled into tiny particles or granules or tablet completely dissolved in water. The disintegration time was calculated in minutes or seconds.

4. Results and Discussion

In this study, we evaluated the physicochemical properties of different brands of levothyroxine are weight variation, hardness thickness, and disintegration. This test was performed to ensure the QC. Specifications of the different brands of levothyroxine are given in Table 1.

Table 1 Specifications of levothyroxine of different brands

No.	Product No.	Batch No.	Mfg. Date	Shelf Life
1	Eltroxin	19D002	April 2019	2 Years
2	Synthroid	1114841	July 2019	2 Years
3	Thyroxine	882G	Aug 2019	2 Years
4	Thyronorm	191126	April 2019	2 Years

4.1. Weight Variation

The calculation of weight variation of multiple brands of levothyroxine (Eltroxin, Synthroid, Thyroxine, and Thyronorm) is shown in Tables 2, 3, and Fig. 1. These tables showed the largest mean value of Eltroxine among all available marketed drugs. All results of multiple brands of levothyroxine (Eltroxin, Synthroid, Thyroxine, and Thyronorm) are within the USP and BP limits shown in Table 4. The weight variation of multiple brands of the same generic is due to the less or more content of active ingredients or excipients, machine error.

Table 2 Statistical calculations of weight variation of different brands of levothyroxine

No.	Product Name	Average weight (mean)	St Deviation	Upper limits (x+3S)	Lower limits (x-3S)
1	Eltroxin	0.1470	0.00124	0.15072	0.14328
2	Synthroid	0.0833	0.00306	0.13236	0.13044
3	Thyroxine	0.1463	0.00158	0.85347	0.08043
4	Thyronorm	0.1043	0.00050	0.1058	0.1028

Table 3 Weight variation calculations of levothyroxine in different brands

Brands name	Calculations
Thyroxine	**20 tablets**
Weight variation mean	0.1463
St.dev	0.00158
UCL	0.85347
LCL	0.0804
Comments	OK
Eltroxin	**20 tablets**
Weight variation mean	0.147
St.dev	0.00124
UCL	0.15072
LCL	0.14328
Comments	OK
Synthroid	**20 tablets**
Weight variation mean	0.0833
St.dev	0.00306
UCL	0.13236
LCL	0.13044
Comments	OK
Thyronorm	**20 tablets**
Weight variation mean	0.1043
St.dev	0.0005
UCL	0.1058
LCL	0.1028
Comments	OK

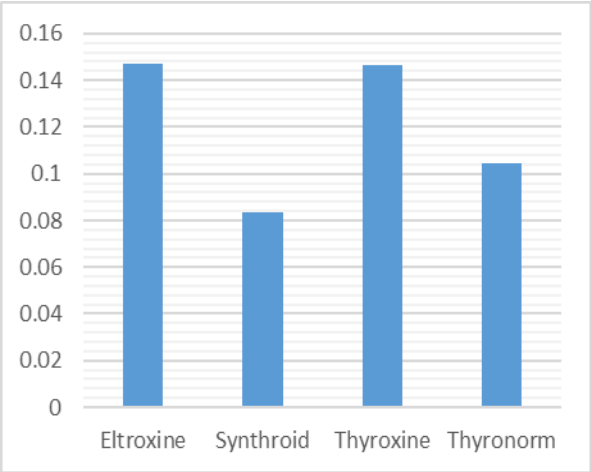

Fig. 1 Weight variation in different brands of levothyroxine

Table 4 Results of weight variation for different brands of levothyroxine

Product name	Batch no.	Results	USP	Deviation from USP
Eltroxin	19D002	0.1470	±10%	Pass
Synthroid	1114841	0.0833	±10%	Pass
Thyroxine	882G	0.1463	±10%	Pass
Thyronorm	191126	0.1043	±10%	Pass

4.2. Thickness of the Tablets

The calculation of thickness of various brands of levothyroxine (Eltroxin, Synthroid, Thyroxine, and Thyronorm) is shown in Tables 5, 6, and Fig. 2. These tables showed the greater mean value of Thyronorm among all four marketed brands of levothyroxine. The mean thickness of various brands of levothyroxine is 0.0410 Eltroxine, 0.0640 Synthroid, Thyroxine 0.0084and 0.1106 Thyronorm. All results of the thickness of multiple brands of levothyroxine (Eltroxin, Synthroid, Thyroxine, and Thyronorm) are within the USP and BP limits shown in Table 7. The thickness of tablets does not affect due to manufacturing like machine compression, speed, etc. thickness of tablet is done to assure the appearance quality of tablets. The thickness of the tablet is a significant QC trial for packaging.

Table 5 Statistical calculations of the thickness of different brands of levothyroxine

No.	Product Name	Thickness (mean)	St. Deviation	Upper limits (x+3S)	Lower limits (x-3S)
1	Eltroxin	0.0410	0.00071	0.04313	0.0388
2	Synthroid	0.0640	0.00745	0.08411	0.0482
3	Thyroxine	0.0847	0.04195	0.11513	10007
4	Thyronorm	0.1106	0.01366	0.1515	0.0696

Table 6 Calculations of the thickness of different brands of levothyroxine

Brands name	Calculations
Thyroxine	**20 tablets**
Thickness mean	0.1048
St.dev	0.00502
UCL	0.1198
LCL	0.0897
Comments	OK
Eltroxin	**20 tablets**

Continuation of Table 6

Thickness mean	0.0410
St.dev	0.00071
UCL	0.043
LCL	0.0388
Comments	OK
Synthroid	**20 tablets**
Thickness mean	0.056
St.dev	0.000745
UCL	0.0841
LCL	0.0482
Comments	OK
Thyronorm	**20 tablets**
Thickness mean	0.1106
St.dev	0.0136
UCL	0.1515
LCL	0.069
Comments	OK

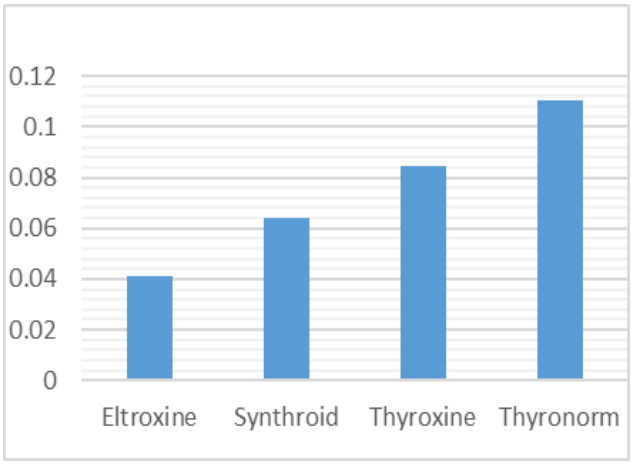

Fig. 2 Thickness of different brands of levothyroxine

Table 7 Result of the thickness of different brands of levothyroxine

Product name	Batch no.	Results	USP	Deviation from USP
Eltroxin	19D002	0.0410	±10%	Pass
Synthroid	1114841	0.0640	±10%	Pass
Thyroxine	882G	0.0847	±10%	Pass
Thyronorm	191126	0.1106	±10%	Pass

4.3. Hardness of the Tablets

The calculation of the hardness of various brands of levothyroxine (Eltroxin, Synthroid, Thyroxine, and Thyronorm) is shown in Tables 8, 9, and Fig. 3. These tables showed the greater value of Eltroxine among all four marketed brands of levothyroxine. The mean of the hardness of various brands of levothyroxine is as follows: Eltroxin 3.8300, Synthroid 3.5400, Thyroxine 3.3700, and Thyronorm 3.6800. All results of the hardness of multiple brands of levothyroxine (Eltroxin, Synthroid Thyroxine, and Thyronorm) are within the USP and BP limits shown in Table 10 and Fig. 3. The hardness of tablets was done to check the broke time of the tablet. The hardness of tablets may be affected by various factors of manufacturing like machine compression, speed, etc.

Table 8 Statistical calculations of the hardness of different brands of levothyroxine

No.	Product Name	Hardness (mean)	St. Deviation	Upper limits (x+3S)	Lower limits (x-3S)
1	Eltroxin	3.8300	0.02739	4.6517	3.0038
2	Synthroid	3.5400	0.20433	4.1529	2.9270
3	Thyroxine	3.3700	0.30741	4.4923	2.4477
4	Thyronorm	3.6800	0.16432	4.1729	318704

Table 9 Calculations of the hardness of different brands of levothyroxine

Brands name	Calculations
Thyroxine	**20 tablets**
Hardness mean	3.33700
St.dev	0.30741
UCL	4.4923
LCL	2.4477
Comments	OK
Eltroxin	**20 tablets**
Hardness mean	3.8300
St.dev	0.02739
UCL	4.6517
LCL	3.0038
Comments	OK
Synthroid	**20 tablets**
Hardness mean	3.33700
St.dev	0.30741
UCL	4.15299
LCL	2.92701
Comments	OK
Thyronorm	**20 tablets**
Hardness mean	3.6800
St.dev	0.16432
UCL	4.17296
LCL	3.1804
Comments	OK

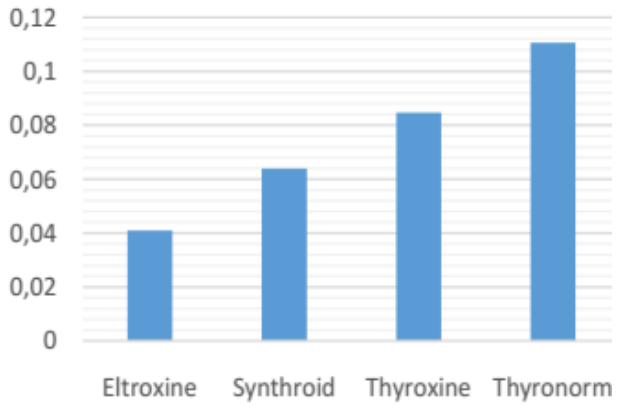

Fig. 3 Hardness of different brands of levothyroxine

Table 10 Result of the hardness of different brands of levothyroxine

Product name	Batch no.	Results	USP	Deviation from USP
Eltroxin	19D002	3.8300	±10%	Pass
Synthroid	1114841	3.5400	±10%	Pass
Thyroxine	882G	3.3700	±10%	Pass
Thyronorm	191126	3.6800	±10%	Pass

4.4. Disintegration Time

The disintegration times of various available brands of levothyroxine are shown in Table 11 and Fig. 4. These table and figure show the greater time of disintegration of Synthroid among the four brands of levothyroxine. According to the USP and BP limits, levothyroxine disintegrates within 45 min. The results showed that Eltroxine disintegrated in 1 min, Synthroid in 4 min and 10 seconds, Thyroxine in 2 min 48 seconds, and Thyronorm in 1, minute, and 43 seconds. All results meet the USP and BP limits.

Table 11 Results of Disintegration test of different brands of levothyroxine

Product name	Batch no.	Results	Limits	Deviation from USP
1	Eltroxin	1 min	15 min	Pass
2	Synthroid	4 min; 10 sec	15 min	Pass
3	Thyroxine	2 min : 48 sec	15 min	Pass
4	Thyronorm	1 min : 43 sec	15 min	Pass

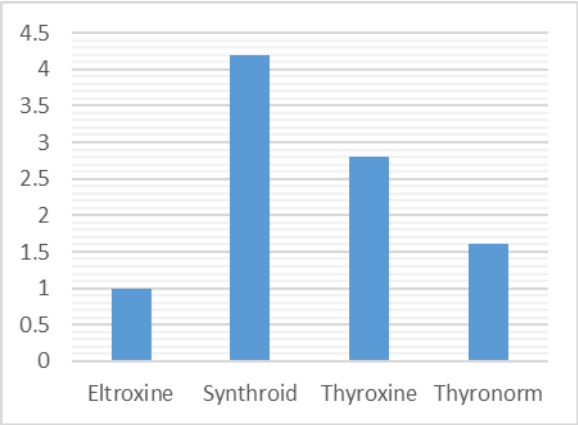

Fig. 4 Disintegration of different brands of levothyroxine

5. Conclusion

5.1. Main Finding

In this research, we conducted a comparative assessment of the physicochemical properties of different available brands of levothyroxine (Eltroxin, Synthroid, thyroxine, and Thyronorm) in Karachi Pakistan. The results of physicochemical properties revealed a few differences, but all results were within the BP and USP limits.

5.2. Comparison with Other Studies

In 2013, the interchangeability of generic vs. brand thyroxin was determined along with Synthroid as standard for comparison. The focus of that research was to analyze and report the therapeutic equivalence of different brands of thyroxin [11]. In 1997, a study was conducted on the comparison of the bioavailability of different brands of thyroxine based on different parameters, including area under the curve or peak concentration of total thyroxin, total triiodothyronine, or free thyroxin index, and concluded that all these brands are interchangeable. The criteria of the FDA for a patient receiving thyroxin treatment are interchangeable in most patients [12]. Some reported studies also stated that multiple brands of thyroxin might also not be interchangeable and suggested that the patients should change their dose while changing brands [13].

5.3. Implications of the Findings

The weight variation, thickness, and hardness of Eltroxin, Synthroid, Thyroxine, and Thyronorm are ± USP/BP upper and lower limits, and the disintegration test results of different brands of levothyroxine are within 15 min as per USP specifications.

5.4. Strengths and Limitations

There is no such study available in the region related to interchangeability and equivalence of levothyroxine though the clinical implications make the drug controversial in terms of clinical equivalency. The study can be further extended toward bioequivalence with more human subjects and more marked available levothyroxine brands.

5.5. Conclusion

This study concluded that the available marked brands are similar in terms of physicochemical properties so we aim that all marketed drugs be equivalent.

5.6. Recommendations and Future Research

All hormone replacement medications should be considered with serious attention as they have negative side effects for patients. We would recommend enhancing the same drug to go with comparative chemical and clinical equivalency through thyroid stimulating hormones in human subjects as a future recommendation.

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