تقييم أقراص تاموكسيفين 10 ملغ لشركات دوائية مختلفة متداولة في سوق الدواء اليمني كمضادة لسرطان الثدي

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الملخص

خلفية البحث: يعدُّ سرطان الثدي أحد أكثر السرطانات شيوعاً عند النساء إِذْ إنَّ امرأة واحدة من بين تسع نساء معرضة للإصابة بسرطان الثدي خلال حياتها.

يتبع تاموكسيفين كيميائياً إلى زمرة ترانس أيزومر ثلاثي فينل ايتيلين واسمه الكيميائي: 2-[4-(1.2- ثنائي فينيل – 1 - بوتينيل) فينوكسي]- ن،.ن- ثنائي ميتيل إيتان أمين. -2 [4-(1,2-diphenyl-1-butenyl)-phenoxy]-N,N-dimethylethanamine والذي يستعمل بشكل واسع كمضاد لسرطان الثدي، وهو أول مضاد للأستروجين أثبت فعاليته كمضاد لسرطان الثدي.

هدف البحث: هدفت هذه الدراسة إلى التقييم الكمي والكيفي لأقراص تاموكسيفين 10 ملغ (Tamoxifen tablets 10 mg) من شركات دوائية مختلفة مسجلة ومسوقة في اليمن.

طرائق البحث: اختيرت خمسة أنواع من أقراص تاموكسيفين 10 ملغ لخمس شركات مسجلة في الهيئة العليا للأدوية.

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طبقت التحاليل الكمية والكيفية لتقييم هذه المستحضرات بالمقارنة مع معياري مرجعي من تاموكسيفين ستيرات. تم اعتماد محتوى معايرة تاموكسفين في الأقراص بحسب معطيات دستور الأدوية البريطاني وهي بحدود (90 – 110 %)، كما تم اعتماد معدل ذوبان لا يقل عن 75 % (Q) من المقدار المعنون على أقراص تاموكسيفين خلال 30 دقيقة بحسب معطيات دستور الأدوية الأمريكي.

النتائج: من خلال تقييم نتائج اختبارات المستحضرات الخمسة من أقراص تاموكسيفين 10 ملغ ظهر أن التحليل الكمي والكيفي كان مطابقاً لمعطيات دستوري الأدوية البريطاني والأمريكي.

الاستنتاج: لم يظهر أي اختلاف معتدٍ به بين نتائج معايرة المادة الفعالة بين مستحضرات الشركات التجارية المسوقة ($p < 0.05$).

الكلمات المفتاحية: أقراص تاموكسيفين، اختبار تحديد الهوية، اختبار التفتت، اختبار الذوبان، موحودية الوزن، المعايرة، جهاز مقياس الطيف الضوئي، سرطان الثدي.

Assessment of Different Commercial Brands of Tamoxifen 10 mg Tablets Marketed in Yemen as Anti-breast Cancer

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Abstract

Background: Breast cancer is one of the most common cancers in women; one of nine women will have breast cancer in her life time.
Tamoxifen is the trans-isomer of a triphenylethylene derivative. The chemical name is: 2-[4-(1,2-diphenyl-1-butenyl)-phenoxy] -N,N-dimethylethanamine.
Tamoxifen is the first anti-estrogen to be used successfully for the treatment of all stages of breast cancer.
Aim: The aim of this study is to evaluate the quality and the quantity of the commercial brands of Tamoxifen 10 mg tablets which are registered and marketed in Yemen.
Methods: We have selected five items of Tamoxifen 10 mg of five different commercial brands, which are registered in Supreme Board of Drugs and Medical Appliance of Yemen.
We have applied the qualitative and quantitative analysis for evaluation these items and comparing with Reference Standard of Tamoxifen citrate. The limit of content of assay of Tamoxifen tablet is (90-110%) (B.P.) and the dissolution content not less than 75 % (Q) of the labeled amount of Tamoxifen tablets is dissolved in 30 minutes (USP).
Results: The results of analysis of these five items of Tamoxifen tablet 10 mg were evaluated and showed that the qualitative and quantitative analysis complied with B.P. and USP requirements.
Concisions: no significant differences between the results of assays of the active ingredient of commercial companies ($p < 0.05$).
Key wards: Tamoxifen tablets, Identification test, disintegration test, dissolution test, Assay, Spectrophotometer, Breast cancer.

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Introduction

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast. Human breast cancer is a clonal disease; a single transformed cell – the product of a series of somatic (acquired) or germline mutations – is eventually able to express full malignant potential[1]. Breast cancer develops as a series of molecular changes in the epithelial cells that lead to ever more malignant behavior. These lesions fall into two groups: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (lobular neoplasia). Not more than 10% of human breast cancers can be linked directly to germline mutations. Several genes have been implicated in familial cases. The female to male ratio is about 150:1[1].

Lots of generic drug products containing Tamoxifen have been registered in Yemen by several pharmaceutical groups or companies and are present in the Yemen market[2]. Quality control of drug is an important subject and plays a main role in the examination of the finished product. The supply of essential drugs of good quality was identified as one of the prerequisites for the delivery of health care at the International Conference on Primary Health Care in alma-Ata in 1978[3].

It was interesting, from a quality control point of view, to perform a comparative analytical evaluation of a trade marked and generic tablet formulations containing Tamoxifen available in the Yemen market.

Materials and Methods

Materials

i- Equipment

Dissolution test unit (Erweka, DT6), Disintegration apparatus (Erweka, Germany), UV/visible Spectrophotometer (Cecil, Ce 1012), Analytical balance (Germany HM-200).

ii- Chemicals and Reagents

Reference standard of Tamoxifen citrate B.P 100%, supplied by Central Quality Control Lab. Sana'a, Yemen. Tamocit® 10mg (Ram pharma), Novofen® 10 mg (Remedica Ltd), Nolvadex® 10mg, (Astrazeneca UK limited), Tamoxifen®10mg (Amriya), Zymoplex® 10mg (Gene-Pharma S.A), purchased from different Yemeni pharmacies.

Analytical grade methanol, Analytical grade HCl manufactured by company (BDH Chemicals LTD Pool England) and supplied by the branch of pharmacy. Aden.

Methods

I- Qualitative Analysis

Identification

The identification test of Reference standard of Tamoxifen citrate and five commercial brands of Tamoxifen (10 mg) tablets was carried out spectrophotometrically at wave lengths (λ) 275 nm[4,5].

Uniformity of weight of tablets

The uniformity of weight of twenty tablets were randomly chosen and weighed individually and the average weight, the standard deviation, and the coefficient of variation percent (CV%) were calculated for each brand of Tamoxifen 10 mg (Table 2)[4].

Disintegration time

The disintegration time of one tablet from each brand of Tamoxifen 10 mg was determined using a disintegrator (Erweka, DT6, Germany) (Table 3)[4].

II-Quantitative Analysis

Dissolution test of Tamoxifen 10 mg tablets

Five commercial brands of Tamoxifen 10 mg were tested and determined the content spectrophotometrically at 275 nm. (Table 6)[4,5].

Apparatus 1 (Basket)

Rotating the basket: 150 rpm

Dissolution medium: 1000 ml (0.02 M HCl)

Time: 30 minutes

Temperature: 37 ^{o}C

Procedure

A USP/NF 23 dissolution apparatus (Erweka, Germany) with six baskets was used for dissolution studies. One tablet was placed in each basket and rotated at 150 rotations/min in 1000 ml of the dissolution medium (0.02 M HCl) at 37 ^{o}C.

The experiment was performed for 30 minutes, during which time samples were withdrawn at suitable time intervals and replaced by an equal volume of dissolution medium, which was kept heated at 37 ^{o}C. Samples were assayed spectrophotometrically at 275 nm. Each determination was performed in triplicate. Calculate the total content of $C_{26}H_{29}NO$ in the medium [4,5]. After the end of the operation for the six tablets tested, the amount of the active ingredients in solution is not less than 75% of the prescribed.

Standard Reference of Tamoxifen

10 mg of Tamoxifen equivalent to 15.2 mg of Tamoxifen citrate

One Tablet diluted in 1000ml 0.02 M HCl

15.2 mg ⟶ 1000ml

The final dilution is 15.2 mg/1000ml = 0.0152mg/ml

Procedure

Weight accurately 15.2 mg of Tamoxifen citrate as standard to 1000 ml volumetric flask. Add 200 ml of 0.02 M HCl, shake foe 15 minutes, Add sufficient volume of 0.02 HCl to produce 1000 ml.

Measure the absorbance of resulting solution at the maximum at about 275 nm[4,5].

Method of assay of Tamoxifen (10 mg) tablets

Weight and powder 20 tablets of Tamoxifen 10 mg. To a quantity of the powder containing the equivalent of 25 mg of Tamoxifen add 100 ml of methanol, shake for 15 minutes and add sufficient methanol to produce 250 ml. Filter, dilute 10 ml of the filtrate to 100 ml with methanol and measure the absorbance of the resulting solution at 275 nm. Calculate the content of $C_{26}H_{29}NO$ taking 325 as the value of A(1%, 1cm) at 275 nm. (Table 5) (Fig 3-8)[4].

Statistical Analysis

One-sample t-test was applied as the statistical method of analysis (SPSS 12.0 computer program) to compare the results of assay of different commercial brands of Tamoxifen 10 mg (Table 6)[6].

Results and Discussions

Five commercial brands of Tamoxifen (10 mg) tablets (Tamocit®, (Ram-Pharma) Novofen®, (Remedica), Nolvadex® (Astrazenca), Tamoxifen® (Amriya) Zymoplex® **(**Gene-Pharma), which marketed in Yemen have been evaluated by Quality Control Specification (B.P, USP). All these drugs are registered in Supreme Board of Drugs and Medical Appliance of Yemen (Table 1).

Qualitative Analysis

Identification

The identification tests of Tamoxifen (10 mg) tablets for five commercial brands were compared with Reference Standard of Tamoxifen citrate and were complied with pharmacopoeias. The maximum light absorption of the solution was obtained at 275 nm, (Fig 2-8)[4,5].

Uniformity of weight of Tablets

The uniformity of weights of 20 tablets for each brand of Tamoxifen (10 mg) were complied with British Pharmacopoeia (Table 2)[4].

Disintegration

All five commercial brands of Tamoxifen (10mg), tablets were complied with test of disintegration time (Table 3). The standard limits for un-coated tablets were not more than 15 minutes[4].

Quantitative Analysis

Dissolution

All five commercial brands of Tamoxifen (10 mg) tablets were complied with USP Pharmacopoeia requirement for dissolution test: Not less than 75 % (Q) of the labelled amount of Tamoxifen tablets is dissolved in 30 minutes at 275 nm. (Table 6, Fig.2)[5]. The dissolution medium was acid (0.02 HCl), so the peak related to the finished product at 275 nm is tri-phenyl ethylene chloride, which give the shape of peak due to high absorption. The % drug release provides a sound foundation for product optimisation and high quality.

Dissolution tests have also been conducted routine in the pharmaceutical development of new drug formulations. Numerous formulation variables are known to affect drug release from hydrophilic matrices. Viscosity grade of polymer, amount of polymer, drug-polymer ratio and nature of the drug used in the tablet system are known to effect drug release from the formulations[7]. The difference in the formulations due to the different in excipients, different concentration of excipients, type of diluents (filler) and other adjacent, amount of disintegration agent, amount of surfactant[7].

By comparing the dissolution results (in vitro) of the five commercial brands of Tamoxifen (10 mg) tablets in 30 minutes[5]. We obtained the results were closer to each other in Tamocit® (Ram-Pharma), (101.69%), and Nolvadox® (Astrazenca, UK) (100.63%), that mean the formulations may be are similar (Table 4).

The dissolution results of two commercial brands of (Novofoen®), (Remedca (115.68%) and Tamoxifen® (Amriya) (118.59%) are closer to each other that mean the formulations may be are similar (Table 4), whereas the result of one commercial brand of Zymoplex® (Gene-Pharma) (133.95%) is differ completely, that means the formulation is widely differed (Table 4)[5]

The difference in the formulations due to the different in excipients, different concentration of excipients, type of diluents (filler) and other adjacent, amount of disintegration agent, amount of surfactant[8].

Assay

The normal range of Tamoxifen (10mg) tablets content is (90-110%)[4].

The assays of different commercials of Tamoxifen 10 mg tablets contents are (96.02%-104.96%) and were complied with pharmacopoeia requirements (Table 5), (Fig 3-8)[4]. That means the drug has good quality and quantity, and best storage condition. Because different factors affect on the quality and quantity of the drug and that affect on the stability such as, humidity, light, and temperatures[8].

The finished product, which is investigated in the assay (methanol) at 275 nm is: Methoxy tri-phenyl ethylene whereas in the dissolution (0.02 N HCl) is Tri-phenyl chloride ethylene[8].

Statistical analysis of the results of assays by one sample T-Test

The results of the assays of different commercial companies were compared statistically by the one-sample t-test. The one sample t-test at the 95% confidence level did not exceed the theoretical values, indicating that there were no significant difference between the results of assays of commercial companies ($p < 0.05$) (Table 6)[6].

Conclusion

All commercial brands of Tamoxifen (10 mg) tablets, Tamocit®, (Ram-Pharma) Novofen®, (Remedica), Nolvadex® (Astrazenca), Tamoxifen® (Amriya) Zymoplex® **(**Gene-Pharma) were complied with the specific requirements for quality control tests of B.P. and USP., namely, the uniformity of weight of tablets, disintegration, dissolution and assay.

The results of the assays of different commercial brands were compared statistically by the one-sample t-test. The one sample t-test at the 95% confidence level did not exceed the theoretical values, indicating that there were no significant difference between the results of assays of commercial companies ($p < 0.05$).

Table (1): Investigated brands of Tamoxifen tablets

Company	Trade Name	Dosage Form	Strength
RAM-Pharmaceutical Industrial Co. Ltd	Tamocit®	Tablet	10 mg
Remedica Ltd limusso Cyprus	Novofen®	Tablet	10 mg
Astrazneca UK limited	Nolvodex®	Tablet	10 mg
Amriya	Tamoxifen®	Tablet	10 mg
Gene Pharma S.A	Zymoplex®	Tablet	10 mg
United Kingdom	Tamoxifen Citrate Reference Standard	Powder	100%

Table (2): Uniformity of weight of tablets of different brands of Tamoxifen tablet (10mg)

No. Of sample	Wt. of tablet in (gm) for Tamocit®	Wt. of tablet in (gm) for Novofen®	Wt. of tablet in (gm) for Nolvadex®	Wt. of tablet in (gm) for Tamoxifen®	Wt. of tablet in (gm) for Zymoplex®
1	0.1230	0.1776	0.1831	0.1800	0.2180
2	0.1226	0.1782	0.1877	0.1777	0.2245
3	0.1211	0.1778	0.1817	0.1842	0.2207
4	0.1224	0.1756	0.1806	0.1757	0.2183
5	0.1223	0.1766	0.1796	0.18107	0.2209
6	0.1186	0.1743	0.1818	0.1781	0.2180
7	0.1177	0.1752	0.1809	0.1816	0.2181
8	0.1247	0.1772	0.1862	0.1827	0.2223
9	0.1242	0.1767	0.1862	0.1795	0.2186
10	0.1187	0.1766	0.1832	0.1769	0.2182
11	0.1279	0.1767	0.1814	0.1831	0.2219
12	0.1230	0.1754	0.1842	0.1802	0.2168
13	0.1246	0.1772	0.1830	0.1791	0.2220
14	0.1237	0.1761	0.1851	0.1847	0.2206
15	0.1240	0.1759	0.1816	0.1782	0.2234
16	0.1246	0.1764	0.1813	0.1741	0.2177
17	0.1183	0.1753	0.1844	0.1805	0.2175
18	0.1245	0.1748	0.1811	0.1836	0.2187
19	0.1210	0.1758	0.1845	0.1782	0.2219
20	0.1218	0.1753	0.1799	0.1816	0.2209
Max	0.1279	0.1782	0.1877	0.1847	0.2364
Min	0.1177	0.1743	0.1796	0.1741	0.2168
Av.wt	0.1225	0.1762	0.1828	0.1799	0.2034
Limit	0.1133-0.1317	0.163-0.1894	0.1691-0.1965	0.1664-0.1933	0.2034-0.2364
Result	Confirm	Confirm	Confirm	Confirm	Confirm

Table (3): Disintegration test of different brands of Tamoxifen tablet (10mg)

Name Of Samples	Tamocit Ram -pharma	Novofen Remedica Ltd	Nolvadex Astrazenca uk	Tamxifen Amriya	Zymoplex Gene pharma S.A
Disintegration time	15min	1min	7min	13min	9min
Limit	Not more than 15 minutes				
Result	Confirm	Confirm	Confirm	Confirm	Confirm

Table (4): Dissolution test of different brands of Tamoxifen tablet (10mg).

No. Of Sample	Tamocit® (Ram – Pharma)	Novofen® (Remedica)	Nolvadex® (Astrazneca, Uk)	Tamoxifen ® (Amriya)	Zymoplex® (Gene-Pharma, S.A)	Reference Standrd
Abs (1)	0.2865	0.2451	0.2559	0.2568	0.3563	0.2612
Abs (2)	0.2244	0.3067	0.2580	0.3238	0.3478	0.2612
Abs (3)	0.2088	0.3248	0.2755	0.3178	0.3514	0.2612
Abs (4)	0.2975	0.3138	0.2634	0.3377	0.3487	0.2612
Abs (5)	0.3055	0.3129	0.2575	0.3108	0.3492	0.2612
Abs (6)	0.2710	0.3097	0.2667	0.3117	0.3460	0.2612
Average of Abs.	0.2656	0.3021	0.2628	0.3097	0.3499	0.2612
Assay	101.696	115.684	100.63	118.593	133.9586	100
Limit	Not less than 75% of the label amount in 30 minutes					
Result	Confirm	Confirm	Confirm	Confirm	Confirm	Confirm

Table (5): Assay of different brands of Tamoxifen tablet (10mg)

No. Of Sample	Tamocit ® (Ram – Pharma)	Novofen® (Remedica)	Nolvadex® (Astrazenec a) UK	Tamoxifen® (Amriya)	Zymoplex® (Gene-Pharma, S.A)	Reference Standrd
Abs (1)	0.3421	0.3218	0.3510	0.3326	0.3210	0.3343
Abs (2)	0.3421	0.3218	0.3510	0.3326	0.3210	0.3343
Abs (3)	0.3421	0.3218	0.3510	0.3326	0.3210	0.3343
Average	0.3421	0.3218	0.3510	0.3326	0.3210	0.3343
Assay %	102.33	96.26	104.99	99.49	96.02	100%
Limit	90-110	90-110	90-110	90-110	90-110	90-110
Result	Confirm	Confirm	Confirm	Confirm	Confirm	Confirm

Table (6): Comparison of assays of Tamoxifen tablets (10 mg) of different brands statistically (One Sample T-test Method)

Ser. No	Products (Tablets)	Labeled amount (mg)	Label found in (mg)	Percent label found
1	Tamocit® Ram –pharma	10 mg	10.23 mg	102.33
2	Novofen® Remedica	10 mg	9.62 mg	96.26
3	Nolvadex® Astrazeneca Uk	10 mg	10.49 mg	104.99
4	Tamoxifen® Amriya	10 mg	9.94 mg	99.49
5	Zymoplex® Gene-Pharma S.A	10 mg	9.60 mg	96.02
St. descriptors				
Mean				99.8180
Std. deviation	±SD			3.8810
Std. Error mean				1.7356
N				5
95% confidence interval of the difference			Significant (One sample test) t =57.510 P < 0.05	

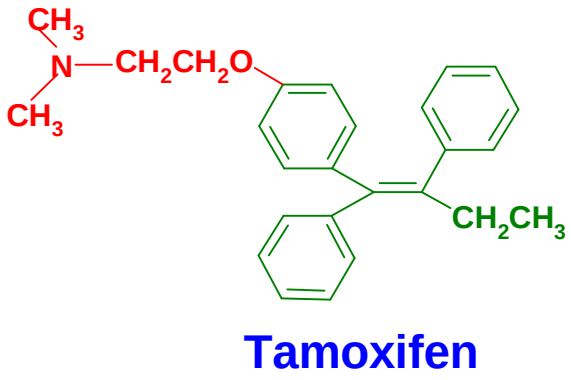

Fig. (1): Chemical structure of Tamoxifen

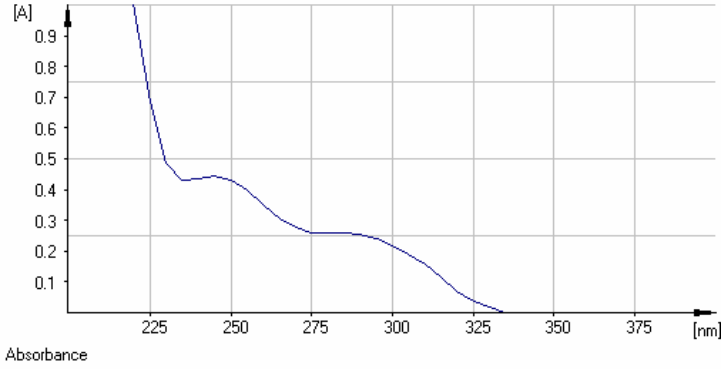

Fig. (2): Identification and dissolution test of Tamoxifen citrate as Reference Standard at 275 nm (B.P.) (Abs. = 0.2612).

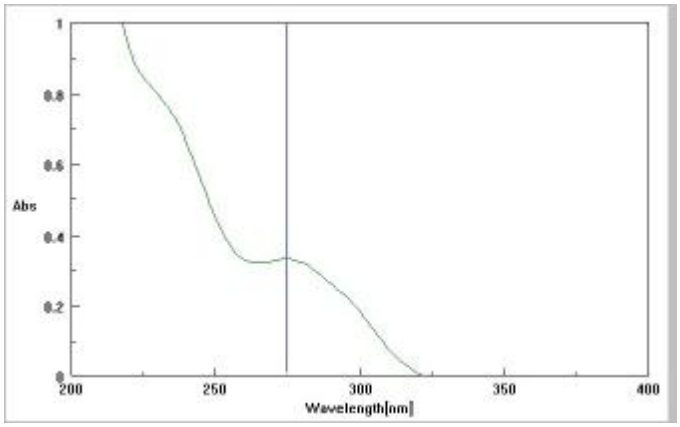

Fig. (3): Identification test and assay of Reference standard of Tamoxifen citrate at 275 nm (B.P), (Abs. == 0.3343)

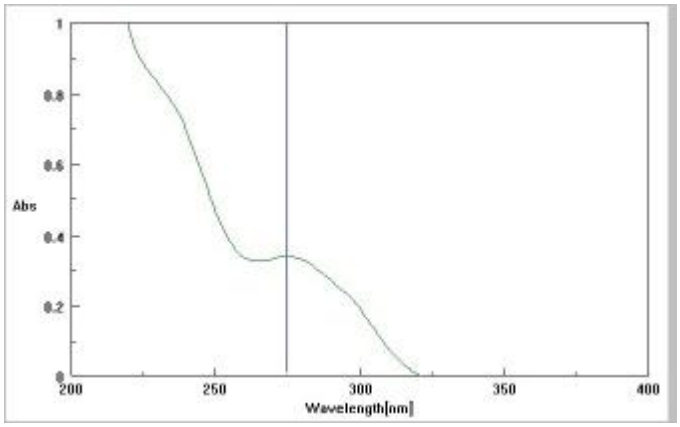

Fig. (4): Identification and assay of Tamoxifen 10 mg tablets (Tamocit®)(Ram) at 275 nm (B.P), (Abs. = 0.3421)

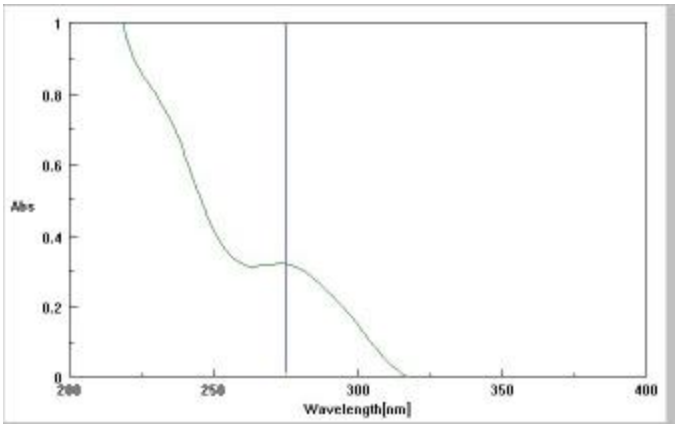

Fig. (5): Identification and assay of Tamoxifen 10 mg tablets (Novofen®) (Remedica) at 275 nm (B.P), (Abs = 0.3218)

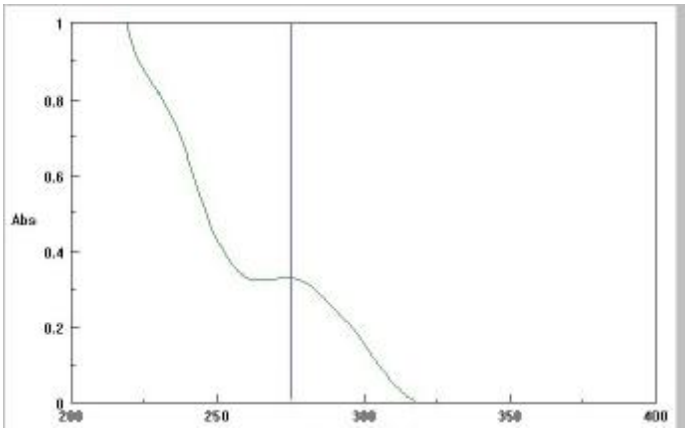

Fig. (6): Identification and assay of Tamoxifen 10 mg tablets (Nolvadex®) (Astrazeneca) at 275 nm (B.P), (Abs = 0.3510)

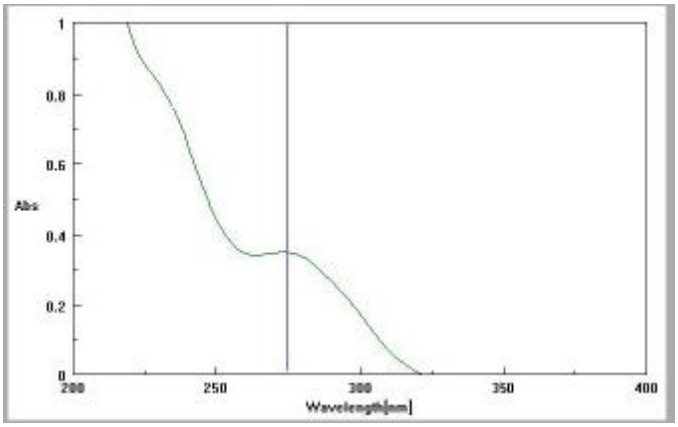

Fig. (7): Identification and assay of Tamoxifen 10 mg tablets (Tamoxifen®) (Al-Amriya)at 275 nm (B.P), (Abs = 0.3326)

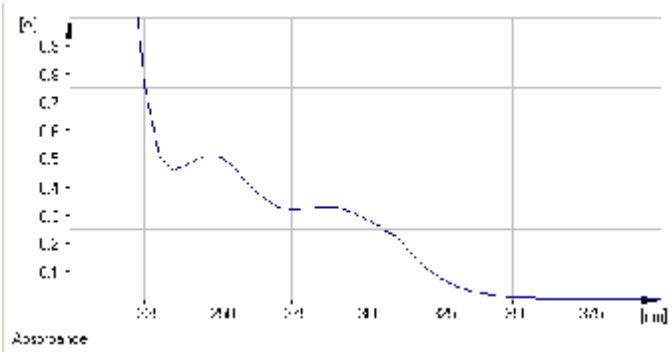

Fig. (8): Identification and assay of Tamoxifen 10 mg tablets (Zymoplex®) (Gene-Pharma) at 275 nm (B.P), (Abs. = 0.3210)

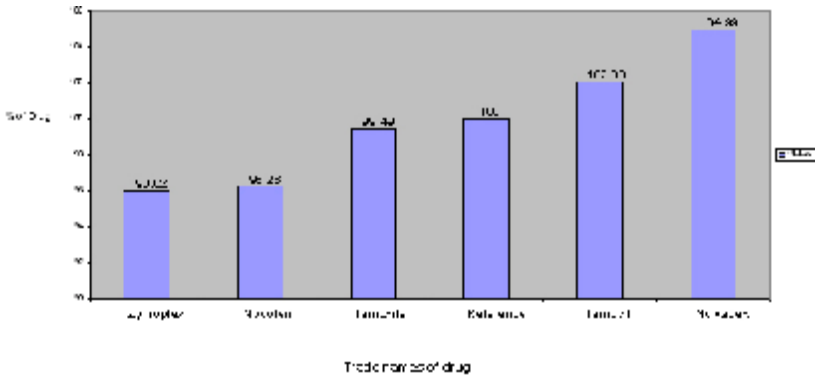

Fig. (9): Coparison of the assay of different commercial brands of Tamoxifen (10 mg) tablets

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