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Comparative *in Vitro* Evaluations of Different Brands of Atenolol Tablets in Libyan Market

Mohamed M. Siaan[1*], Massud A. S. Anwair[2], Fathi Sadek[3], Anisa Elhamili[2]**

[1]Department of Industrial Pharmacy, Faculty of Pharmacy, Tripoli University - Libya

[2]Department of Medicinal and Pharmaceutical Chemistry, Faculty of Pharmacy, Tripoli University - Libya

[3]Department of Laboratory Medicine, Higher Institute for Medical Profession, Tripoli, Libya

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Abstract: Continuation of our research studies of various pharmaceutical products in the Libyan market in order to monitor their quality, effectiveness, safety and safety of patients.[1,2,3] So, in this study we focused on comparative in vitro evaluations of different brands of atenolol tablets and this study included some of the specifications that should be provided in medicine from appearance, thickness, diameter, weight variation, hardness, friability, disintegration time, dissolution, tensile strength, thickness and diameter, where these investigations have become widely accepted as a method of controlling of drug products and we have Prepared of standard calibration curve of atenolol by methanol for the assay and other standard calibration curve of atenolol by 0.1NHCL for the dissolution and the results data were compared them with scientific references and we found that all the visual inspection testing for all the atenolol tablets of the 3 brands were in a good condition, and each individual tablet was free from cracks and the tablets color, surface smoothness & polish were uniform on whole surface for the samples tested.

Keywords: Atenolol tablets, Methanol, Hydrochloric acid**,** Sodium chloride**,** oven, Spectrophotometer and desiccators.

INTRODUCTION

Pharmaceutical Drug is a chemical substance that has known biological effects on humans or other animals used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being and may be used for a limited duration, or on a regular basis for chronic disorders[4-7.] Active pharmaceutical ingredient (API) means any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions inhuman beings and a finished dosage form such as tablets, capsules or solutions that contains an active pharmaceutical ingredient, generally, but not necessarily, in association with inactive ingredients Quality is the ability of a drug product to satisfy the users need and their main attributes are identity, strength and purity.

Safety of the quality or condition of being safe means freedom from danger injury, or damage and safety issues can arise if toxic impurities are present, which could cause side effects to the patient.[8,9] The efficacy of the preparation must remain constant (or change only within the limits specified by legal provisions) until the date of expiration. Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by the patient and can be measured by the rate of changes that take place in the pharmaceutical dosage forms.[10]

Tablets are solid preparations each containing a single dose of one or more active ingredients and are obtained by compressing uniform volumes of particles. The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in the desired location and to have its chemical integrity protected to the point. Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance.[11] Oral drug delivery remains the preferred route for administration of various drugs. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain evasion and most importantly the patient compliance.

Atenolol is a synthetic, beta1-selective (cardioselective) adrenorecept or-blocking agent which recognized and extensively prescribed as first choice of drugs in the treatment of majority of the hypertension population. It may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin and α-methyldopa[12]. The conventional formulation of these drugs is rapidly dissolved in upper gastric intestine and produces peak plasma concentration within 1 to 4 hours and then declines quickly[13]. Besides being one of the most widely used b-blockers clinically, it has often been used as a reference drug in randomized controlled trials of hypertension and also atenolol is available worldwide under various trade names by several generic pharmaceutical manufacturers.[14-16]

MATERIALS AND METHODS

All chemicals and solvents, reagents used in the present study were of analytical grade purchased from different companies such as methanol, spectrosol®, pharmaceutical grade, BDH Limited Poole England; Hydrochloric acid, WINLAP, made in UK.; Sodium chloride COTUSAL, made in Tunisia, and all the solvents were used after distillation.

All the samples were kept at temperature of 40± 2 °C, atenolol blisters were left inside an oven at 40 ^{0}C and 75 ± 5% relative humidity.

Analyses were carried out at time 0, after storage of 2, 4, 16, 20, 26 weeks and all tests including friability, hardness, disintegration and dissolution were measured by PHARMA TEST, Apparatebau. GmbH. Siemensstrasse 5 D-63512 Hainburg (Germany).

Preparation of standard calibration curve of atenolol by methanol for the assay: Atenolol reference standard 25mg was accurately weighed and dissolved in 50 ml methanol. From the above solution, a 1ml was diluted to 100 ml with methanol to produce 5µg/ml of atenolol reference standard. Suitable aliquot of this stock solution of atenolol was diluted with methanol to obtain 5-140 µg/ml of atenolol reference standard and their absorbance was determined at 275 nm. So, the standard curve was plotted between absorbance and concentration.

Preparation of standard calibration curve of atenolol by (0.1N) HCL for the dissolution: Atenolol reference standard 25mg was accurately weighed and dissolved in 50 ml(0.1N) HCL, and from the above solution a1ml was diluted to 50ml with(0.1N) HCL to produce 10µg/ml of atenolol reference standard. Suitable aliquot of this stock solution of atenolol was diluted with methanol to obtain 10-160 µg/ml of atenolol reference standard and their absorbance was determined at 275 nm. So, the standard curve was plotted between absorbance and concentration.

Weight variation: 20 tablets randomly and weighed individually, the average weight was calculated and individual weight was compared to the average weight. The tablet passes the test if not more than two of the individual weights deviate from the average weight by more than ± (10 %, 7.5 %, 5 %) according to the weight of the tablet and none deviate by twice the limit[17].

Friability: The % friability of the tables of each brand calculated by the use of Friability tester and friability should be less than 1%. 20 tablets were taken randomly, loose dust was removed and tablet samples were weighed accurately then placed in the friabilator. After the given number of rotations (100 rotations) loose dust was removed from the tablets and the finally tablets weight were determined, [18] then percentage friability was determined by using the following formula:

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \text{ X } 100$$

Weight loss of the tablets should be NMT 1%, and should be no any broken tablet.[21]

Hardness: The hardness of 20 tablets was determined by diametric compression using a hardness tester apparatus and the average hardness of the tablets was obtained. [18, 19]

Disintegration test: Disintegration time was measured by using 6 tablets from each brand using distilled water as disintegration medium, a disc was added to each tube and the apparatus was operated for 30 minutes, then the disintegration time for each tablet was observed and recorded[18. 19].

Dissolution test (In-vitro dissolution study): The release rate of atenolol tablet was studied by using a USP type II dissolution test apparatus at 100 rpm for 1 hr. in 900 ml simulated gastric fluid (0.1N HCl) as dissolution medium at 37°C ± 0.5°C. and after 5, 10, 15, 30, 45 and 60 minutes, 10 ml samples were taken out and 10 ml volume of fresh 0.1N HCL was added to keep volume of

dissolution medium constant. Then each sample was analyzed using UV-Vis. spectrophotometer at 275 nm and percent drug release was calculated.[17]

Assay: 20 tablets were powdered and transferred to a 500 ml flask by adding 300 ml of methanol, the resulting suspension was heated to 60 ^{0}C, shake for 15 minutes. The solution was cool and diluted to 500 ml with methanol, then filtered through a filter paper (Whatman GF /C), a suitable volume of the filtrate was diluted with sufficient methanol to produce a solution containing 0.01% w/v of atenolol and the absorbance of the resulting solution was measured at 275nm, using a UV-Vis spectrophotometer and percent content was determined[18, 19].

RESULTS & DISCUSSION

The results of this study can be explained and Illustrative in detail and accurate as follows

1. Evaluation of Appearance: Results of the evaluation of appearance for the 3 different brands of atenolol tablets are given in the table (1) which infer that the selected tablets of different brands were orange in color, circular, biconvex in shape and having smooth surface texture. Atenolol 50 embossed on one surface T 50 but atenolol 100 embossed on one surface T 100, while hypoten embossed on one surface H, 34, one groove. From the visual inspection testing it can be found that all atenolol tablets of the 3 brands were in a good condition, and each individual tablet was free from cracks and the tablets color, surface smoothness & polish were uniform on whole surface for the samples tested.[20]

Table 1: Appearance of atenolol brands

Brand names	Shape	Color	Surface texture	Picture
Atenolol	Circular Biconvex	Orange	Smooth	
Hypoten	Circular Biconvex	Orange	Smooth	
Atenolol	Circular Biconvex	Orange	Smooth	

2. Test for tablet thickness and diameter: The thickness and diameter test results for the 3different marketed brands of Atenolol tablets are given in the **table (2)** which infer that all the tablets of the 3 brands were had uniform thickness and diameter. Add to that hypoten was the highest diameter, atenolol 100 was the highest thickness and atenolol 50 was the lowest one due to weight.

Table 2: Geometrical dimensions of atenolol brands.

Brand names	Average thickness (mm)	Average diameter (mm)
Atenolol 100	0.073	0.407
Hypoten	0.070	0.420
Atenolol 50	0.056	0.324

3. Test for weight variation: The weight variation test results for the 3 different marketed brands of atenolol tablets are shown in the **table (3)** and from the tensile strength calaculation we can reported that the

Tensile strength: $T = \frac{2F}{\pi d h}$

Hypoten is the best one due to the highest tensile strength = 248.27 then atenolol 100 = 201.73 and the lowest one atenolol 50 =182.19.

Based on the resulted data, it can be noticed that all brands pass the test but atenolol 100 and hypoten had nearly the same tablet weight (0.421, 0.414) respectively while the weight of atenolol 50 was about the half due to their weight.

Table 3: Weight variation of atenolol brands

Brand names	Average weight/ gm	Limit	Number of tablets falling outside the range
Atenolol 100	0.421 ±0.004	*±5%	Nil
Hypoten	0.414 ±0.009	*±5%	Nil
Atenolol 50	0.211 ±0.003	*±7.5%	Nil

*Standard deviation (n=20)

4. Test for tablet friability: Friability % for the 3 different brands of atenolol tablets are given in **table (4)** which inferred that all the tablets of the 3 brands were within the limit (less than 1%) hypoten had the lowest % and atenolol 50 had the highest %.

Table 4: Friability % for different atenolol brands.

Brand names	% Friability
Atenolol 100	0.34
Hypoten	0.12
Atenolol 50	0.45

5. Test for hardness: The hardness test results for the 3 different brands of atenolol tablets are given **table (5)** which shown that all tablets of the 3 brands had satisfactory hardness (more than 4 kg). The hardness of atenolol100 and hypoten is very similar to each other but atenolol 50 has about the half of their hardness. Other than ability to withstand shock during handling, tablet hardness can also indirectly affect the rate of disintegration and dissolution of a tablet[21]. If the tablet is too hard, it will

not achieve the specified dissolution rate and it also will not disintegrate completely within the specified time[22].

Table 5: Hardness of different atenolol brands/kilogram

Brand names	Average hardness	Standard deviation (n=20)
Atenolol 100	9.41	±0.276
Hypoten	11.46	±0.870
Atenolol 50	5.19	±0.333

6. Test for Disintegration: Based on BP (2009), the film-coated tablet needs to disintegrate completely within 30 minutes and uncoated table needs to disintegrate completely within 15 minutes. Although all atenolol brands under investigation were coated tablets, they disintegrated very fast (less than a minute in case of atenolol 50 and the maximum disintegration time was 3.46 minutes for Hypoten). Therefore all atenolol brands under investigation passed this test. The disintegration test results for the three different brands of atenolol tablets are given in the **table (6)**.

Table 6: Disintegration time of atenolol brands

Brand names	Disintegration time / minutes	Standard deviation (n=6)
Atenolol 100	2.08	±0.884
Hypoten	3.46	±0.727
Atenolol 50	0.26	±0.078

7. Test for Dissolution: The absorbance and concentration measurement results of different brands of atenolol in 0.1N HCL are given in the **table (7)** while Standard calibration curve of atenolol in 0.1NHCL is shown on **figure (1)** and dissolution results of atenolol brands at zero time were given on **table (8), figure (2)**, and all these results show that all atenolol brands were within the limit (after 30 minute 80% of drug should be released). The dissolution test measures the time required for a given percentage of a drug substance in a tablet to go into solution under specific set of conditions and dissolution can be described as a tool that can provide valuable information about the bioavailability of a drug product. It has been well documented that the rate of which a drug dissolve from its intact of fragmented dosage forms in the gastrointestinal tract often partially or completely controls the rate of drug absorption, and in some cases, in vitro dissolution test results have been related to bioavailability. Dissolution testing has become widely accepted as a method of controlling of drug products, there are now dissolution test requirements in the USP. However, although there are many examples of good correlation between dissolution studies and bioavailability, it is widely held that dissolution testing cannot completely replace either invivo bioavailability or bioequivalency testing.

Table 7: Absorbance and concentration of atenolol in 0.1N HCL.

Conc. /µg /ml	0	10	20	30	40	60	80	120	140	160
Abs./ nm	0	0.042	0.078	0.117	0.151	0.224	0.301	0.455	0.528	0.611

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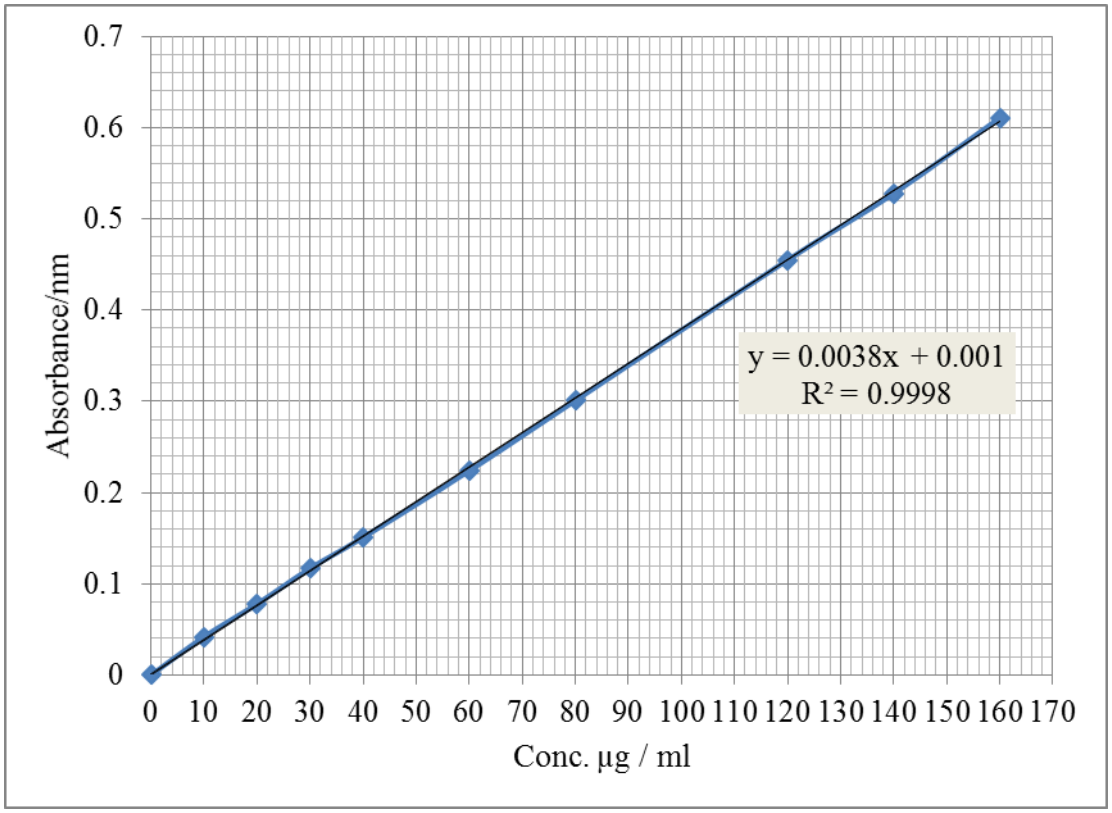

Figure 1: Standard calibration curve of atenolol in 0.1N HCL.

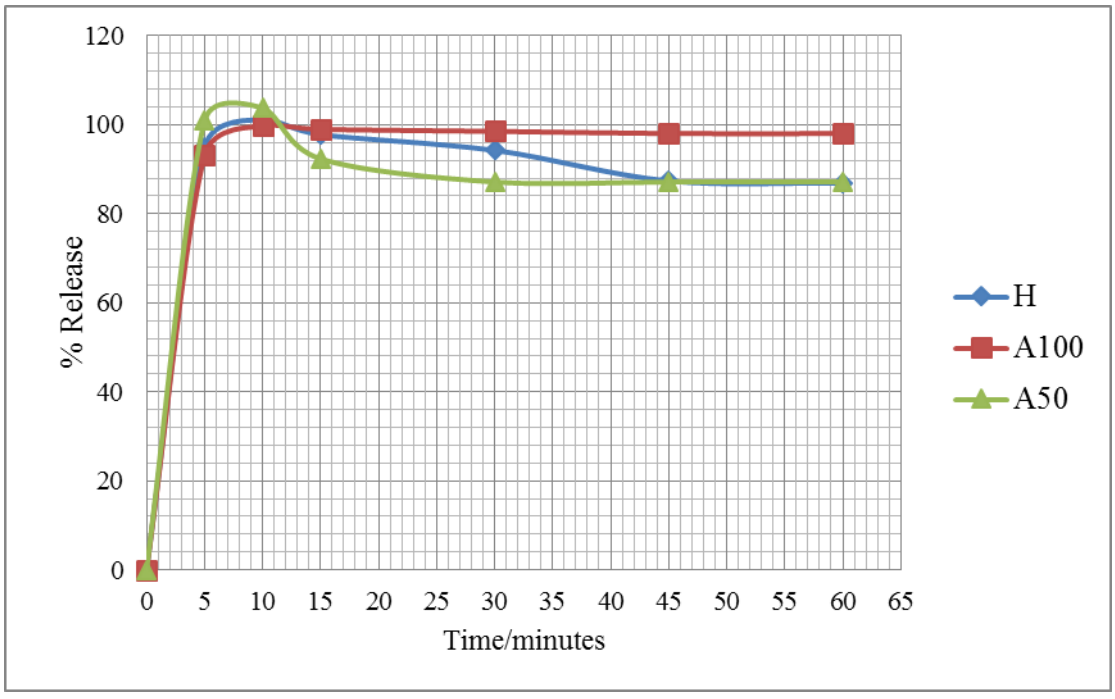

Figure 2: Dissolution Profile for different atenolol brands in 0.1N HCL at 0 time.

Table 8: Dissolution profile for different brands at 0 time

Atenololbrands Time/minute	Abs./nm Hypoten 100mg	Con. of Hypoten (ug/ml)	% release of Hypoten	Abs./nm Atenolol 100mg	Con. of Atenolol100 ug/ml	%release of Atenolol 100mg	Abs./nm Atenolol50mg	Con. of Atenolol 50 ug/m	% release of Atenolol 50 mg
5	0.401	105.53	94.97	0.393	103.42	93.08	0.213	56.05	100.89
10	0.427	112.37	101.13	0.421	110.79	99.71	0.219	57.63	103.74
15	0.413	108.68	97.82	0.418	110.00	99.00	0.195	51.32	92.37
30	0.398	104.74	94.26	0.416	109.47	98.53	0.184	48.42	87.16
45	0.369	97.11	87.39	0.414	108.95	98.05	0.184	48.42	87.16
60	0.367	96.58	86.92	0.414	108.95	98.05	0.184	48.42	87.16

8. Test for Content of Active Ingredient (Assay): Based on the data recorded from **Table 9, 10,** and calibration curve was plotted as concentration Vs. absorbance **(Figure 3),** it clears infer that the content of atenolol in tablet of different brands were within the limits prescribed by BP., and on comparing all the brands the content of atenolol is highest in hypoten. The content uniformity test of single-dose preparations is based on the assay of the individual contents of active ingredient of a number of single-dose units to investigate whether the individual contents are within the limits set. British Pharmacopoeia stated that for single-dose preparation of tablets, the preparation will complies with the test if each individual drug content is between 92.5 percent and 107.5 percent[22].

Table 9: Data of standard calibration curve of atenolol in methanol.

Conc. µg/ml	0	5	10	15	20	40	60	80	100	120	140
Abs. nm	0	0.025	0.049	0.072	0.092	0.180	0.274	0.374	0.465	0.568	0.647

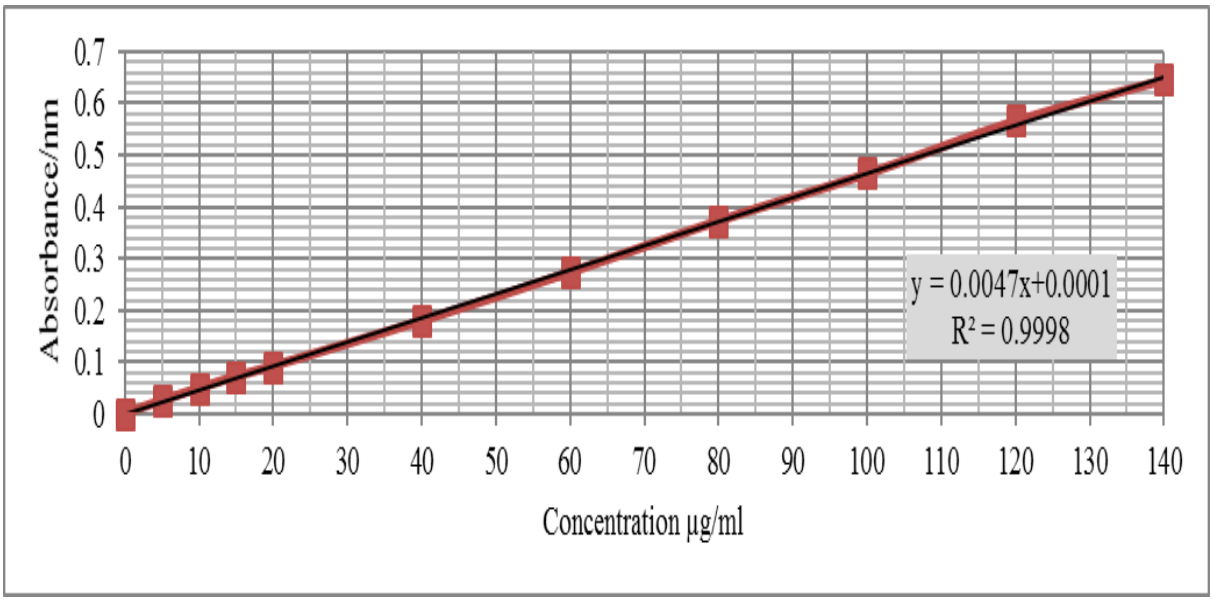

Figure 3: Standard calibration curve of atenolol in methanol.

Table 10: % Content of active ingredient.

Brand names	Abs. of Atenolol/nm	Con. of Atenolol (µm/ml)	% Content of atenolol
Atenolol 100	0.490	104	104
Hypoten	0.502	106	106
Atenolol 50	0.477	101	101

CONCLUSIONS

From the results of study, we can be concluded that all the 3 atenolol brands were passed the test and within the limit, and all the brands were had uniform thickness and diameter, add to that hypoten was

the highest diameter, atenolol 100 was the highest thickness and atenolol 50 was the lowest one due to weight. The content atenolol of different brands were complied with the test and within the limits prescribed by British Pharmacopoeia (BP), and United State Pharmacopoeia (USP).

Future Work: Our research team will continue this research study to complete the rest of the specifications to be provided in the medicines for these and other types and we will publish our results in future bulletins.

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Corresponding author: Mohamed M. Siaan,

[1]Department of Industrial Pharmacy, Faculty of Pharmacy, Tripoli University - Libya

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