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Research Article

COMPARATIVE PHYSICAL STUDIES OF ATENOLOL BRANDS AVAILABLE IN LIBYAN DRUG MARKET

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ABSTRACT

Atenolol is a cardioselective beta1-adrenergic receptor blocking agent prescribed for treatment of hypertension, angina pectoris and cardiac arrhythmias. However, there are many Atenolol brands marketed in Libya. The objective of this study was to evaluate the quality of five commercial Atenolol (100 mg) products available on the Libyan market. We carried out a survey on the price of all Atenolol tablet products and assessed their quality. To assess quality, all products were examined visually for their organoleptic properties, tested for weight uniformity, friability, disintegration, and moisture content assayed. We carried out a physical comparison of all Atenolol tablet products and assessed their quality. To assess quality, all products of Atenolol such as: Atenolol tablets, Actavis United Kingdom, Totamol tablets WOCKHARDT , United Kingdom, Atenolol Normon Spain, Atenolol Film Coated tablets, BRISTOL, United Kingdom and Hypoten tablets, HIKMA Amman–Jordan. Based on our testing procedure, all Atenolol five brands were showed the fulfilment of the compendial specification for uniformity of weight, disintegration and limit of moisture content, except in case of hardness test all the brands showed softer than Hypoten tablets. All the brands are within their expiry dates but there is major difference in price.

Keywords: Atenolol, β-blockers, Hypertension, Friability, Disintegration test, Libyan market.

INTRODUCTION

Atenolol [4-(2-hydroxy-isopropylaminopropoxy)-phenylacetamide], is one of the most popular and most widely used selective β1 blocker. Atenolol is used in the management of hypertension [1], angina pectoris, cardiac arrhythmias, and myocardial infarction [2]. It may also be used in the prophylactic treatment of migraine [3]. In hypertension atenolol is given by mouth in a dose of 50 to 100 mg daily, as a single dose, although 50 mg daily is generally adequate. The full effect is usually evident within 1 to 2 weeks [4].

Atenolol is used alone or in combination with other medications to treat high blood pressure. It also is used to prevent angina (chest pain) and improve survival after a heart attack. Atenolol is in a class of medications called beta blockers. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure [5].

About 50% of a dose is absorbed after oral doses. Peak plasma concentrations are reached in 2 to 4 hours. Atenolol has low lipid solubility. It crosses the placenta and is distributed into breast milk where concentrations higher than those in maternal plasma have been achieved. Only small amounts are reported to cross the blood-brain barrier, and plasma-protein binding is minimal. The plasma half-life is about 6 to 7 hours. Atenolol undergoes little or no hepatic metabolism and is excreted mainly in the urine. It is removed by haemodialysis [6].

Dissolution test was carried out in four different medium to establish bioequivalence among the different brands. The primary goal of dissolution testing is to use as a qualitative tool to provide measurement of the bioavailability of a drug. Generic drugs are copies of innovator drug products. So they are promoted for use in practice because they are usually less expensive than the innovator products, thereby improving access to life-saving drugs, especially in developing countries [7].

Studies were done to examine the physico-chemical stability of atenolol tablets stored in a compliance aid at room temperature, and at elevated temperature and humidity to simulate practice conditions. Tablets at room temperature in original packaging, in compliance aids and Petri dishes remained the same in appearance and passed physico-chemical tests. Tablets exposed to 40°C with 75% relative humidity in compliance aids passed tests for uniformity of weight, friability and chemical stability but became pale and moist, softer than tablets in the original packaging more friable compared with other tablets, and failed the tests for disintegration (>15 minutes) and dissolution (only 15% atenolol released at 30 minutes) Although chemical stability was unaffected, storage in compliance aids at 40°C with 75% relative humidity softened atenolol tablets, prolonged disintegration time and hindered dissolution which could significantly reduce bioavailability. This formulation could be suitable for storage in compliance aids at 25°C, but not in hotter, humid weather [8].

Materials and Methods

Materials and Instruments

Atenolol tablets produced by Actavis " United Kingdom" (Batch number OKB061004), Totamol tablets produced by WOCKHARDT " United Kingdom " (Batch number OLT1937CP4), Atenolol Normon produced by Laboratorios Normon , S.A " Spain " (Batch number D-5), Atenolol Film Coated tablets produced by BRISTOL " United Kingdom " (Batch number EP0071009), Hypoten tablets produced by HIKMA Pharmaceutics " Amman – Jordan " (Batch number 7611), Distilled Water.

Instruments

Sensitive Balance "Sartorius" Germany, Friabilator "Pharma Test" type: PTF E, Germany,Hardness tester "Pharma Test" type: PTB E, Germany, Disintegration apparatus "Pharma Test" type: PTZ, Germany.

Methods

The study was carried out in October 2012 at Faculty of Pharmacy, department of Pharmaceutics, University of Tripoli, Libya.

We have subjected all five brands of Atenolol such as: Atenolol, Totamol, Atenolol Normon, Atenolol Film Coated tablet and Hypoten tablets for Fulfilment of the compendia specification for visual inspection, uniformity of weight, friability hardness, disintegration, and moisture content assay.

Visual Inspection of Atenolol tablets.

Atenolol tablets were inspected visually and compared in respect to the visual characteristics, such as: color, clarity, shape, surface, diameter & thickness.

Determination of Weight Variation of Atenolol tablets

To assess weight uniformity, 20 tablets of each brand were weighed individually. The percentage deviation of the individual tablets from the mean was determined according to compendial requirements of the United States Pharmacopeia (USP) [9].

The accepted limit: The weight of not more than two of tablets differ from mean weight by more than the percentage listed, and no tablet differs by more than double that percentage .

Average = (weight of 20 tablets) ÷ (No of tablets)

% Deviation= (weight of tablet – average) ÷ average ×100

Average weight of tablet (mg)	% Deviation
130 or less	± 10.0
From 130 to 324	± 7.5
More than 324	± 5.0

Determination of Friability of Atenolol tablets

Tablet strength was evaluated by the friability test [9]. This test is important to evaluate the resistance of coated or uncoated tablet upon exposure to mechanical shock or attrition. A number of 10 tablets of each brand of Atenolol were weighed and placed in the tumbling apparatus where they were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After a 100 rotation for 4 minutes the tablets were weighed and the loss in weight indicates the ability of the tablets to withstand all these kinds of pressure applied on the packages [9].

% Friability = (initial weight-final weight) ÷ (initial weight)× 100

Friability values are usually considered satisfactory when the product exhibits a weight loss of less than 1 %.

Determination of Hardness of Atenolol tablets.

This test normally consists of breaking or crushing the tablet by application of a compressive load, Hardness of tablets was evaluated by using hardness tester. A number of 10 tablets of each brand of Atenolol were subjected to this test. One tablet was placed in its position. The machine turned on till the tablet broken down and pressure applied was read in Kg, the same steps were repeated with other 9 tablets.

The average of the ten readings was calculated [9].

Limit: Force in kg must be within the range from 10 to 20 kg, and only one is allowed to be outside the limit.

Determination of Disintegration time of Atenolol tablets

The disintegration time of Atenolol tablets brands was determined according to the procedure reported in the USP [9]. In summary, 1 tablet is placed in each of the 6 tubes of the basket and the disintegration apparatus was operated using water maintained at 37 °C. At the end of the time limit specified in the USP (15 minutes for uncoated tablets and 30 minutes for coated tablets); all of the tablets should disintegrate completely.

Limit: Disintegration time is within 15 minutes.

Determination of Water Content (Karl-Fischer)

The compartments of the reaction cell were filled with electrolyte reagent for the micro determination of water and performed the coulometric titration to a stable end-point. The prescribed amount of the substance to be examined was introduced into the reaction cell, then stirred for 30 s. The value from the instrument's output was estimated and calculated the amount of water that is present in the substance. When appropriate to the type of sample and the sample preparation, perform a blank titration as shown in Figure 1.

RESULTS AND DISCUSSION

Hypertension is the most widely distributed cardiovascular diseases in Libyan regions. Atenolol is one of most used β-blockers in Libya as the first line in treatment of hypertension.

The generic brands that were used in this study had a significant variation in their prices. The data showed Atenolol Film Coated tablets BRISTOL and Atenolol tablets, Actavis, UK are more cheaper than Totamol tablets WOCKHARDT , UK, Atenolol Normon Spain and Hypoten tablets, HIKMA Amman–Jordan, whereas the active ingredient as well as the excipient used should fulfill the specification of USP/BP.

Evaluation of organoleptic properties of Atenolol tablets)The shape, color, clarity & Thickness) and presence of black spots or breached edges of all tablet products were examined visually. The visual inspection of local the imported products showed no sign of defects in all tested tablets as shown in Table1.

Figure 1: Water Content (Karl-Fischer) Test.

Evaluation of physicochemical properties of Atenolol tablets, to assess weight uniformity; tablets of each brand were weighed individually. The percentage deviation of the individual tablets from the mean was determined according to compendial requirements of the United States Pharmacopeia (USP) [9]. Weight uniformity of tablets were attained by all tested products within the limit of percentage deviation, Data are shown in Table 2.

Tablet strength was evaluated by the friability test. This test is important to evaluate the resistance of uncoated tablet upon exposure to mechanical shock or attrition. For friability, ten tablets of each atenolol brands were weighed and subjected to abrasion. The apparatus was set at 24–26 revolutions/min and percentage powder loss was determined. The friability results were within the pharmacopeial limits a maximum loss of powder not more than 1% w/w with a range of 0.0044%–0.145% w/w. The assay of the all products was in conformity with the USP requirement as shown in Table 2.

The disintegration time of Atenolol tablets was determined according to the procedure reported in the USP [9]. At the end of the time limit specified in the USP (15 minutes for uncoated tablets and 30 minutes for coated tablets); all of the tablets should disintegrate completely. The disintegration time for all Atenolol tablets was within the pharmacopoeial limits, ranging from 1.0 min to 11.5 min.

Hardness test of the selected brands (Atenolol, Totamol, Atenolol Normon and Atenolol film coated) were failed to pass through this test with variable negative results below the limit 10 kg. Except in case of Hypoten tablets are hard enough and the data showed above the limit of 12-16 kg as shown in Tables 2. The negative result of Atenolol four brands (Atenolol, Totamol, Atenolol Normon and Atenolol film coated) and became softer than Hypoten tablets, may be due to exposed those brands to temperature or humidity [8]. Therefore, We subjected these brands to the moisture content test by using Karl-Fisher method [10] .

In the present study the investigated products of Atenolol such as: Atenolol tablets, Actavis United Kingdom, Totamol tablets WOCKHARDT, United Kingdom, Atenolol Normon Spain, Atenolol Film Coated tablets, BRISTOL, United Kingdom and Hypoten tablets, HIKMA Amman–Jordan were subjected to karl-fischer assay to examine whether these product exposed to humidity. The results showed the percentage of water content of each brand as determined by Karl Fischer method in Figure 2. Our results exhibited the normal limit of moisture as compared to standard range of 0.4 to 9.90 % as shown in Table 2.

Our investigation was revealed the correlation between the price of Atenolol tablets were imported from different manufactures and comparative physical studies to indicated that the products have same drug molecules with approximately same pattern specification for

uniformity of weight, hardness, disintegration, friability and content assay

Previous researches in this area have shown that the post-marketing evaluation of drug products is important to develop the confidence for manufacturer in order to ensure the safety and efficacy of the product [11, 12]. As well as this kind of studies help the healthcare people in interpretation between different brands of same generic.

All the brands are within their expiry dates but there is major difference in price. Regardless of price, generic products should be compared with innovator for its quality and efficacy.

Table 1: Visual inspection results of tested Atenolol five brands.

	Color	Clarity	Shape	Surface	Diameter (mm)	Thickness(mm)	Tablet Type
Atenolol	Off white	Clear	Round	Smooth	9.69 mm	4.42 mm	Tablet
Totamol	Orange	Clear	Round	Smooth	10.9 mm	4.49 mm	Tablet
Atenolol Norman	Pale Orange	Clear	Round	Rough	11.20 mm	5.73 mm	Coated Tablet
Atenolol Film-coated	Off white	Clear	Round	Smooth	8.21 mm	3.95 mm	Film- coated tablet
Hypoten	Orange	Clear	Round	Smooth	10.65 mm	4.84 mm	Tablet

Table 2. Fulfilment of the compendia specification for visual inspection, uniformity of weight, friability hardness, disintegration, and moisture content assay.

	% Weight variation test	**% Friability test**	**% Hardness test**	**% Disintegration test**	**% Moisture Content test**
Atenolol	PASS	PASS	Failed	PASS	3.11
Totamol	PASS	PASS	Failed	PASS	6.21
Atenolol Norman	PASS	PASS	Failed	PASS	6.38
Atenolol Film-coated	PASS	PASS	Failed	PASS	6.33
Hypoten	PASS	PASS	PASS	PASS	6.03

CONCLUSION

The post-market monitoring is very crucial for effective clinical outcome. The study has emphasized that physical equivalence indicated that the products have same drug molecules with approximately same pattern specification for uniformity of weight, hardness, disintegration, friability and content assay [13]. By making fine tunings in the survey equivalence study we can reduce the time, cost and unnecessary exposure of healthy subjects to medicines and finally to market the quality generic drug products with good prices deals.

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