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Research Article

A COMPARATIVE STUDY FOR EVALUATION OF FIVE FORMULATIONS OF AMLODIPINE 10 MG TABLETS MARKETED IN LIBYA

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ABSTRACT

Objective: Amlodipine is a calcium channel blocking agent prescribed for treatment of hypertension. However, there are many Amlodipine brands marketed in Libya, with different quality and prices The objective of this study was to evaluate the quality of five commercial Amlodipine (10 mg) products available in the Libyan market such as: Amlor (Pfizer, Morocco), Amlodipine (Bristol, UK), Amlodipine (Blue pharm, Portugal), Amlodipine (Sandoz, UK) and Amady (Ajanta Pharm, India).

Methods: To assess quality, all products were examined visually for their organoleptic properties, weight uniformity test, friability, hardness, disintegration test, dissolution test and IR were assayed. We carried out a physical comparison of all Amlodipine tablet products and assessed their quality. The second part of study was carried out a survey upon mentioned formulations of Amlodipine tablets. This survey was including: (45) pharmacist (9) Physicians and (32) Patients volunteers. All the brands are within their expiry dates but there is major difference in price.

Results: All the tested five brands were equivalent and complying with the official tests for weight variation, friability, disintegration and dissolution tests. The Hardness of the tablets was failed to pass this test and the range was between 3.8 kg to 11.0 kg of five brands according to USP specifications. The friability test between 0.054% to 0.223%. All formulations were disintegrated between 35 second to 2.15 min. The tested brands were identical according to their dissolution evaluation. The percentage content of active ingredient of five brands of Metformin tablets showed values within the monograph specifications (75-94.8%). Infra-Red (IR) spectroscopic investigations were revealed no any difference between Amlodipine five brands and showed identical peaks compared to the reference. The simple Survey forwarded to patients , pharmacists and Physicians to explore their opinion, the most preferable brands is Amlodipine (Bristol) 41%, 44% & 59%respectively. They have chosen Amlodipine according to effectiveness & healthiness.

Conclusion: All the available brands in local market of Libya are having, with in the specified quality range and considerably, can be chosen according to good quality and cost, to improve the therapeutic benefit and patient compliance without interchangeability.

Keywords: Amlodipine, IR, friability test, disintegration, dissolution test & survey.

INTRODUCTION

Cardiovascular diseases are increasing rapidly in the developing world. Hypertension is one among the most important modifiable risk factors for cardiovascular disease [1], it affects approximately one billion people in the worldwide. Treatment of high blood pressure can reduce cardiovascular mortality and morbidity [2].

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It is indicated for the treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina. The chemical name of amlodipine is 3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4- dihydropyridine-3,5-dicarboxylate [3] .

According to the Biopharmaceutical Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability [4]. Amlodipine falls under the BCS Class I, rapidly soluble and highly permeable drugs. Biowaivers were granted for BCS Class I drugs by FDA and WHO [5].

It was reported that the most commonly prescribed drugs to cardiovascular patients in the internal medicine ward was amlodipine, in which 34.88 % (n=45) were amlodipine and the most common cardiovascular disease condition among the patient was hypertension [6].

Similarly, in another study it was reported that 67% of total drugs for hypertension was calcium channel blocker, 97.14% was amlodipine and the rest 2.86 % was nifedipine [2]. Being the most popular drug among the calcium channel blocker, it needs a special surveillance that assures the high quality of drugs ultimately help to enhance the quality of life in developing countries.

Amlodipine is listed in World Health Organization (WHO) model list of essential medicines as antihypertensive medicine in 5 mg tablet [6]. .

Amlodipine is described as slightly soluble in water in different Pharmacopoeias [3], [7]. The experimental water solubility for amlodipine is 75.3 mg/L [6]. The lowest solubility in the pH range from 1 to 6.8 at 37 °C is 1 mg/mL [8]. Within the gastrointestinal pH range, amlodipine is an ionized compound (weak base). The pKa of amlodipine is about 8.6 at 25 °C [8]. Dosage form strength is expressed in mg of salt and is not equivalent to the free base.

When an active pharmaceutical ingredient is absorbed to an extent of 85% or more, it is considered “highly permeable.” Amlodipine’s absolute bioavailability is 60–65%, but its permeability is classified as “high” due to metabolite excretion in urine (90–95%).

Post market medicines monitoring serves as a confidential tool to judge the quality, therapeutic efficacy and safety of medicine. Improvement of existing regulations and product development can be accelerated with the help of information obtained from such monitoring. In this research physical parameters of commercially available amlodipine tablets were evaluated. Moreover, no such evaluation on amlodipine of the local market was carried out before. These facts directed our interest to assess the quality of some commercially available amlodipine tablets in the Libyan market with special emphasis on disintegration and dissolution

study due to their mammoth significance in predicting bioavailability and product quality [9]. .

Materials

Amlodipine tablets such as (i) Amlor (Pfizer, Morocco), (ii) Amlodipine (Bristol, UK), (iii) Amlodipine (Blue pharm, Portugal), (iv) Amlodipine (Sandoz, UK) and (v) Amady (Ajanta Pharm, India, Amlodipine besylate as standard drug was brought from India and Hydrochloric acid 0.01N pH 1.2.

Instruments

For samples weighing an analytical balance Sensitive Balance "Sartorius" Germany, The hardness test was determined using Hardness tester "Pharma Test" type: PTB E, Germany, Disintegration Tester Disintegration apparatus "Pharma Test" type: PTZ, Germany, The Friability test was done by using Friabilator "Pharma Test" type: PTF E, Germany, and a Dissolution rate test, ERWEKA DT600 dissolution apparatus, Germany was used. All UV spectroscopic measurements were performed using UV spectrophotometer (Specord 200). IR Spectroscopy was done by using Infra-red spectrophotometer.

Methods

The study was carried out in May 2019 at Faculty of Pharmacy, department of Pharmaceutics, University of Tripoli & Tripoli Centre of Drug & Food quality Control and specifications Tripoli/Libya.

We have subjected all five brands of Amlodipine tablets such as (i) Amlor (Pfizer, Morocco), (ii) Amlodipine (Bristol, UK), (iii) Amlodipine (Blue pharm, Portugal), (iv) Amlodipine (Sandoz, UK) and (v) Amady (Ajanta Pharm, India for Fulfilment of the compendia specification for visual inspection, uniformity of weight, friability hardness, disintegration, Dissolution test as well as Infra-red spectroscopy .

Visual Inspection

Amlodipine tablets were inspected visually and compared in respect to the visual characteristics including:- Colour, clarity, shape and size. The size in diameter of five tablets from each brand were measured and the average was taken.

Uniformity of Weight

Twenty tablets of each formulation were weighted individually by using a Sensitive Balance, and the mean weight was calculated, and the percentage (%) deviation of the individual tablets from the mean was determined. according to United States Pharmacopeia (USP). 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.

Hardness Test

The machine was calibrated and then one tablet was placed in its position. The machine turned on till the tablet breaks down and pressure applied was in Kg, the same steps were repeated with other nine tablets. The average of ten reading was calculated to determine the crushing strength of tablets..

Friability Test

A number of 10 tablets of each brand of amlodipine were weighted and placed in the Friabilator apparatus "Pharma Test" type: PTF E, Germany at 100 revolutions for 4 min. The tablets were deducted and weighed again then percent of weight loss was recorded. The friability of the tablets were then calculated using the following Formula :

% 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%.

Disintegration Test

The disintegration test was carried out by using Disintegration apparatus. Six tablets from each formulation were subjected to disintegration test. One tablet was placed in each of the six tubes of the basket. Then disks were added to each tube of the basket. The time taken for the last tablet to disintegrate completely was recorded in minutes.

The disintegration time limit for uncoated tablet should be within 15 minutes, While for coated tablet should be disintegrated within 30 minutes according to the USP specifications.

Dissolution Rate Determination

Dissolution rates were determined using (ERWEKA DT600 dissolution apparatus, Germany). One tablet was put in each of the compartments of the apparatus using 500 mL of 0.01N Hcl medium at 37 ± 0.5 °C. The paddle was rotated at 75 rpm. Ten millilitres of sample was drawn at intervals of 10, 20, & 30 minutes with 10 mL bulb pipette. A fresh 10 ml dissolution medium was replaced after each sampling to maintain the sink conditions.

Each of the withdrawn sample was filtered with syringe filter 0.45µm, the filtrate diluted. The absorbance was measured at λ max 237nm using UV spectrophotometer (Specord 200). The concentration was determined against standard solution having a known concentration of Amlodipine in the same medium. The percentage of drug released is calculated using the given formula.

% of drug release value = Conc (mg/ml) of sample / Actual concentration) * (purity of standard) * (Molecular weight of Amlodipine /molecular weight of Amlodipine besylate)*100

% of sample At 30 min = (0.02646mg/ml / 0.0200mg/ml) * (0.993) * (408.9/567.1) * 100 = 94.72 %

Infra-red spectroscopy

Infrared spectra were obtained on IR spectrometer. The samples were prepared in KBr 10-15 mm diameter discs(1-2 mg of the substance to be examined was titrated with 300-400 mg of finely powdered and dried potassium bromide). IR Spectroscopy is used for recording spectra in the region of 650-4000 cm-1 .

Method of Survey

The study was carried out in August 2019 at: Tripoli Medical Centre & Tripoli Central Hospital, Tripoli/Libya.

We have subjected the survey of all five brands of Amlodipine such as: Amlor (Pfizer, Morocco), Amlodipine (Bristol, UK), Amlodipine (Blue pharm, Portugal), Amlodipine (Sandoz, UK) and Amady (Ajanta Pharm, India). It was subjected for (45) pharmacist (9) Physicians and(32) Patients volunteers in different regions of Tripoli/Libya. The survey was including : several question to assess the best brand should be available in Libyan market for sales. Our survey concerned the type and nature of questionnaire including: (a) Dispensing an alternative brands, (b) Dispensing only one of these brand in the prescription, (c) The quality of these brands equal to new ones and (d) Switching for brands to another. The questioner was directed to the physicians was included : (a) The choice of one of these brands, (b)The reason of this choice, (c) If there is changing from brand to anther and about if there is any side effects. Finally, the questioner was directed to the Patients volunteers was included: (a) The best choice of these brands, (b) The reason of choosing one of these

Brands, & (c) The most side effects by using one of these brands.

Based on our testing procedure, we have collected all the data of our questionnaire and statistically were analysed and tabulated. Our survey data were plotted in figures to show the related results.

RESULTS AND DISCUSSION

Amlodipine is a widely prescribed oral anti-hypertensive agents. Several brands of Amlodipine tablets are available in the Libyan market leading to a confusion of their quality and prices. The objective of the present study is to make a comparative evaluation of five different brands of Amlodipine which are commercially available in Libyan market. They were subjected to number of quality control tests in order to assess their biopharmaceutical equivalence. The branded products of Amlodipine tablets evaluated for various physiochemical properties. The size of tablets was in the range of (8.04 to 12 mm in diameter) with all five brands. There is no significant difference between the batches of the brands as shown in Table 1. The uniformity of weight for the five brands of Amlodipine tablet gave values that compiled with USP specification and deviated less than 7.5 % from the mean value as shown in Table 3. The result of tablet friability test showed that all the brands tested had impressive friability values ranging 0.054% to 0.223% w/w According to USP, no batch should have a friability value greater than 1% w/w as showed in Table 4. Using hardness tester, the strength of the tablets was tested. Hardness of the tablets was in the range between 3.8 kg to 11.0 kg of five brands. Unfortunately, All of the tablets failed this nonofficial test according to USP specifications, this is may be due to the moisture content as shown in Table 2.

Table 1: Visual inspection of tested five brands of Amlodipine Tablets

Brand name	Color	Type of tablet	Shape	Size (mm) Diameter
Amlor (PFIZER)	White	Coated	Circular	10.6
Amlodipine (BRISTOL)	White	Coated	Circular	10.6
Amlodipine (BLUE PHARMA)	White	Coated	Longitudinal	12.0
Amlodipine (SANDOZ)	White	Uncoated	Oblong	10.6
Amady (AJANTA PHARMA)	Yellow	Uncoated	Circular	8.04

Table 2: The hardness test of five brands of Amlodipine Tablets

Brand name	Result	Comment
Amlor (PFIZER)	11kg	Failed
Amlodipine (BRISTOL)	11 kg	Failed
Amlodipine (BLUE PHARMA)	1.5 kg	Failed
Amlodipine (SANDOZ)	3.8 kg	Failed
Amady (AJANTA PHARMA)	4.2 kg	Failed

Table 3. Weight variation of five brands Amlodipine Tablets

Brand name	Results	Comment
Amlor (PFIZER)	0%	pass
	0.73%	
	-0.98%	
Amlodipine (BRISTOL)	0.50%	pass
	1%	
	0.25%	
Amlodipine (BLUE PHARMA)	0.82%	pass
	-0.41%	
	0.41%	
Amlodipine (SANDOZ)	0.327%	pass
	0.61%	
	-0.30%	
Amady (AJANTA PHARMA)	0%	pass
	0.55%	
	-0.55%	

Table 4: Friability test of five brands of Amlodipine Tablets

Brand name	Results	Comment
Amlor (pfizer)	**0.073%**	**PASS**
Amlodipine (bristol)	**0.072%**	**PASS**
Amlodipine (blue pharma)	**0.054%**	**PASS**
Amlodipine (sandoz)	**0.223%**	**PASS**
Amady (ajanta pharma)	**0.099%**	**PASS**

The observed disintegration times for all the brands of Amlodipine investigated was less than 30 min. The fastest disintegration tablets were of Blue pharma brand was 35 second, while the slowest one was Amlodipine Pfizer brand was 2.15 minutes. The various brands could have employed different disintegrates to improve the penetration of aqueous liquids as shown in Table 5. The in-vitro drug release characteristics of the developed marketed tablets were studied. The dissolution of all five brand of Amlodipine tablets is slowly dissolving amount is greater than 28 % at 10 min in acidic media with pH 1.2. Amlodipine then showed Rapid release at 30 min the amount is dissolved greater than 75 % in the same media.

Furthermore, It is important to note, that Amlodipine Blue pharm has greater release 94 % than the other brands, which is correlated to Its disintegrations time was very short 35 seconds compared to the other brands as shown in Table 6 and Figure1. Conversely, To previous study [9], the release showed faster at 10 min in the same media.

Table 5: Disintegration time of five brands of Amlodipine Tablets

Brand name	Result (Minutes)	Comment
Amlor (PFIZER)	02:15	Pass
Amlodipine (BRISTOL)	01:12	Pass
Amlodipine (BLUE PHARMA)	00:35	Pass
Amlodipine (SANDOZ)	01:25	Pass
Amady (AJANTA PHARMA)	01:29	Pass

Table 6. Dissolution efficiency, % released for five brands of Amlodipine

Time (Minutes)	Amlor (PFIZER) % Drug released	Amlodipine (BLUE PHARMA) % Drug released	Amlodipine BRISTOL % Drug released	Amlodipine (SANDOZ) % Drug released	Amady (AJANTA PHARMA) % Drug released
0	0.0	0.0	0.0	0.0	0.0
10	29.0	28.3	39.4	32.9	34.3
20	60.8	73.7	63.7	63.7	62.6
30	87.7	94.8	75.5	84.5	77.3

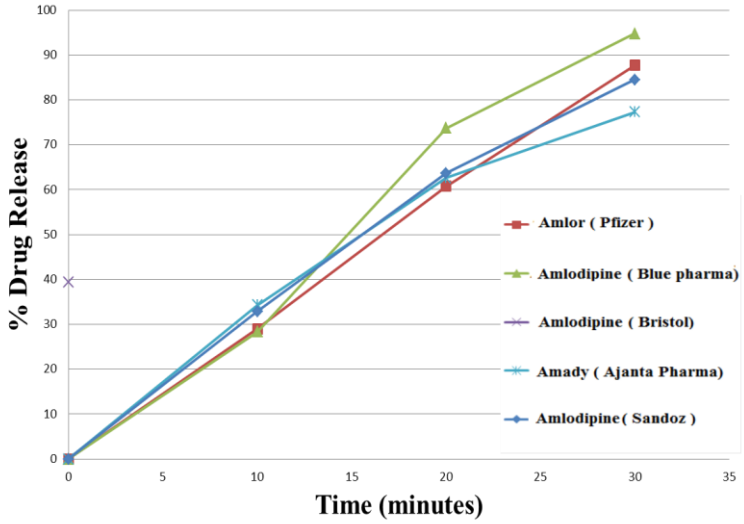

Fig. 1: Dissolution profiles of five commercial product of Amlodipine 10 mg Tablets, at 75 rpm (Paddle), with dissolution medium pH 1.2 Hydrochloric acid 0.01N, at 37 ± 0.5°C

The IR spectra revealed an investigation of the physical-chemical properties of the drug substance, alone and in combination with excipients of five different brands. Assessment of possible compatibilities between the drug and different excipient is an important part of formulation. The principal absorption peaks of Amlodipine appear at 3310 to 3350 cm−1 due to the Secondary amine, a stretching of the primary amine group at 3500 to 3400 cm−1, due to the presence of 1770 to 1780 cm−1 and 1750 to 1735cm−1 which are indicated to phenyl and ester groups respectively. A peak occurs at 1225 to 1200 cm−1 indicates to ether and 500 to 600 cm−1 to the Chloride as shown in Figure 2. This suggests that there is no incompatibility between drug and excipients. Other studies have also reported compatibility of amlodipine besylate with excipients like sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide and camphor [10].

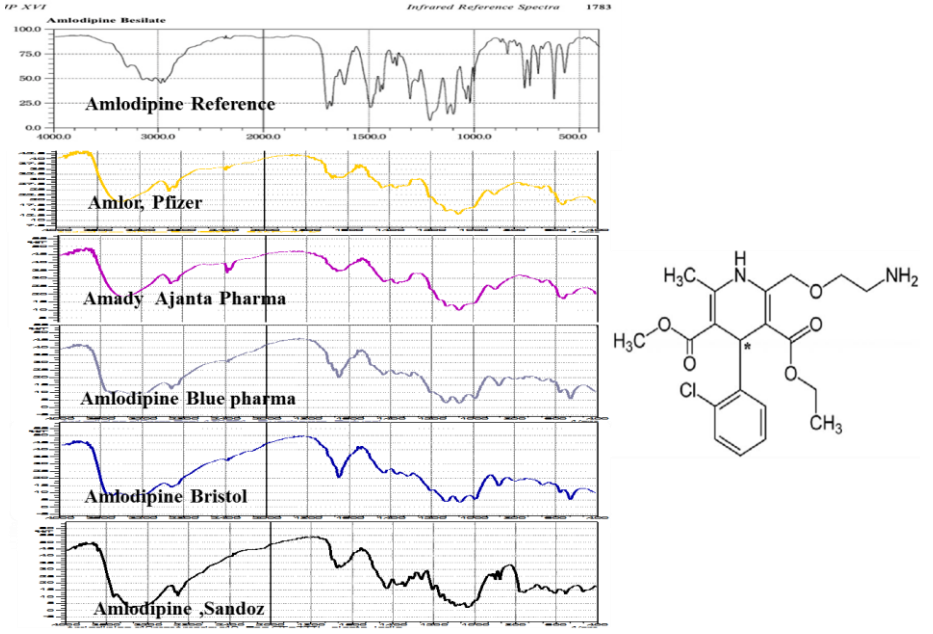

Fig. 2: Spectrum of Amlodipine provided by Drug reference & five brands of Amlodipine Tablets

The simple Survey forwarded to patients, pharmacists and Physicians to explore their opinion. The most preferable brands by pharmacist and physician are Amlor (Pfizer) 41% and Amlodipine (Bristol) 41% & 44% respectively, while patients are preferred Amlodipine (Bristol) 59% and 25% (Sandoz) as shown in Figure 3.

On the other hand, the survey showed 57% of pharmacists claim the quality of local not as innovative and 51% said to dispense only the prescribed rather than the alternative Amlodipine brand as shown in Figure 4.

The survey also revealed about 66% of physicians follow their patients if they use any alternative brands. On the other hand 33% of physicians prescribe only generics.

The common side effects of Amlodipine were monitored through survey on a few number of 32 patients treated with different brands, 90 % of them claimed a notable swelling in their legs and ankles, but 10 % said Stomach pain or fatigue is produced. For this reason, We found 55% of physicians are caring about if they face any side effects.

Furthermore, The Survey revealed about 56% & 43% of patients have chosen Amlodipine according to healthiness with less feeling of its side effects and good efficacy respectively.

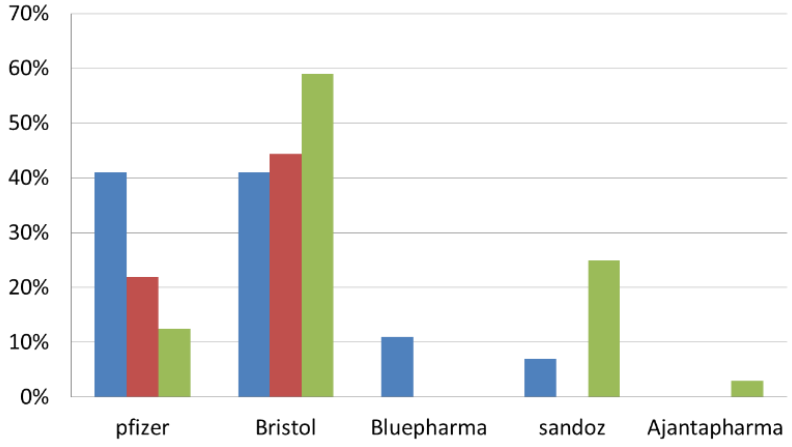

Fig. 3. Comparative opinion study of five different brands of Amlodipine

Tables : (A) Pharmacist (B) Physician & (c) Patient

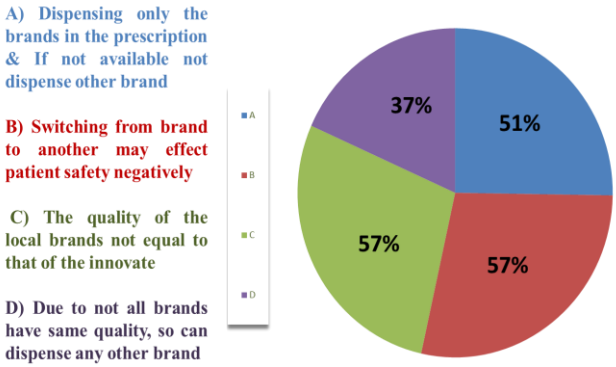

Fig. 4: The point of view of some pharmacists about Amlodipine brands interchangeability in Libya.

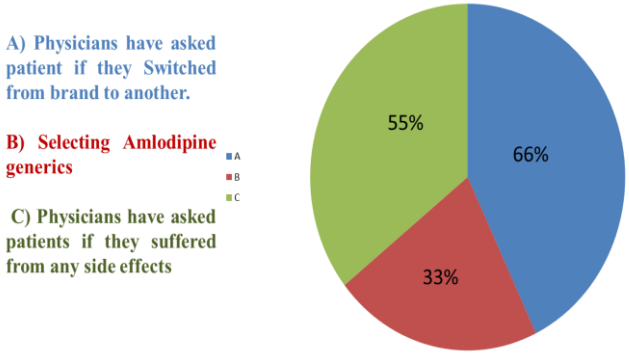

Fig. 5: The point of view of some Physicians about brands Amlodipine brand interchangeability in Libya

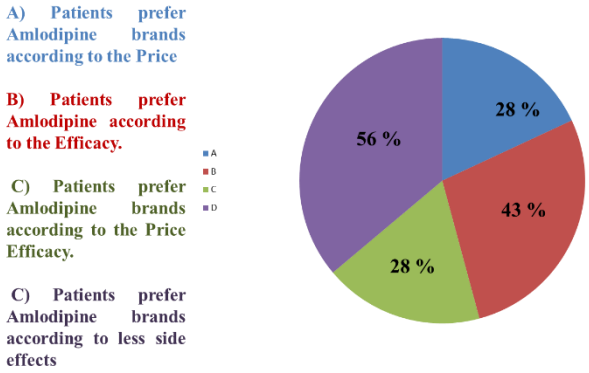

Fig. 6: The point of view of some patients about brands Amlodipine brands interchangeability **in Libya.**

Conclusion

The evaluated Amlodipine brands are available in local Libyan market fulfill biowaiver criteria for drugs containing BCS Class I active pharmaceutical ingredients except in term of hardness. Moreover, the test products showed compatibilities between the drug and different excipient. By making fine tunings in the survey equivalence study, we can Consider good quality and cheap products, suggest more likely to improve the therapeutic benefit and patient compliance.

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Conflict of interest

The author declares that they have no conflict of interest.

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