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Original Article

IN VITRO ASSESSMENT OF PHYSICOCHEMICAL PARAMETERS OF FIVE GENERICS AMLODIPINE BESYLATE TABLETS MARKETED IN YEMEN

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ABSTRACT

Objective: The present paper aims to evaluate the quality of five different brands (local and imported) of oral film-coated tablets of generic Amlodipine besylate 5 mg marketed in Sana`a-Yemen, through physiochemical parameters.

Methods: Different physicochemical parameters, including the uniformity of tablet weight, hardness, thickness, disintegration time, and an assay of active ingredients, were conducted to validate the quality of generics Amlodipine Besylate 5 mg according to USP specification.

Results: From the obtained results, it was observed that all the brands of Amlodipine Besylate 5 mg have passed the tests and met the specifications of USP. Results of weight variation, hardness, thickness, and disintegration time were ranged from-3.8 % to+5.13 % to-1.25 % to+3.25 %, 5.06±0.31 to 13.21±1.5, 2.682±0.04 to 3.676±0.01 and 25 s to 2 min: 30 s, respectively. The dissolution test and the assay results of all the brands are also ranged within the acceptable label claim 93.7±2.24 to 98.4±0.85 and 93.22±0.38 to 100.15±0.33, respectively. However, there is no relation was found between the disintegration time and the dissolution test.

Conclusion: According to the finding, all the selected Amlodipine Besylate 5 mg brands are met pharmacopeia standards and USP specifications. Therefore, the local and imported Amlodipine Besylate 5 mg can be used safely to get the desired therapeutic efficiency.

Keywords: Amlodipine, Quality control, United stat of pharmacopeia, Hypertension

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INTRODUCTION

Over the past several decades, the term hypertension has been widely used in most of medical cases. Hypertension (also known as high blood pressure) is the potential risk factor for A) cardiovascular, such as congestive heart failure, myocardial infarction, stroke, ruptured aortic aneurysm, and B) renal disease [1, 2]. Many factors can be attributed to the risk of hypertension, such as high sodium intake, unhealthy diet habits, stress, poor physical activity, and alcohol composition [3, 4]. Katherine T Mills *et al.* had reported that 31.1 % of adults had high blood pressure as the highest percentage was found in the low-and mild-income countries (31.5%) while the high-income countries showed low percentage (28.5%) [3, 5]. However, many pharmaceutical companies started to manufacture different types of medicine to control the high blood pressure and the adversities for these pharmaceutical products through printed bills, electronic media and newspapers. These products may be i) branded (original and proved by FDA), ii) unbranded (generics called a faithful imitation of a mature drug but not approved by a patent, had the same active ingredients and expected to show bio-equivalent to the branded drug) and iii) sometimes, fake [6]. Hence, quality control investigations are an important strategy to access the medicines as interchangeable drugs before distributing them to the population, especially in low-income countries and cities under conflicts or war.

Amlodipine was patented by Pfizer under the brand name Norvasc. Amlodipine, a third-generation dihydropyridine, is a long-acting L-calcium channel blocker used worldwide, in the treatment of hypertension and angina pectoris. It decreases blood pressure by the relaxation of vascular smooth muscles and vascular dilatation mechanism [7]. After the expiration of the Amlodipine patent in 2007, several of generic versions became available [8]. 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 and its structure is represented in fig. 1. Amlodipine is considered a moderate drug release [9] and is available in three strength forms: 2.5, 5, and 10 mg.

Fig. 1: The chemical structure of Amlodipine

To improve the solubility and enhance the bioavailability of the Amlodipine, different formulations of Amlodipine conjugated salts have been generated and commercially available. Some of these forms are: Adipate [10], Nicotinate [11], and Besylate [12, 13]. On the other hand, combination drugs are used to increase the effectiveness of the hypertension medication along with decreasing the undesired effects are also reported [14-16]. In 2010, sheikh *et al.* developed a tablet formulation of S-(-)-Amlodipine Besylate chiral separation drug and Nebivolol Hydrochloride for better management of hypertension [17]. In 2012, Sukhavasi *et al.* published a formulation of amlodipine besylate tablets with Fenugreek seed mucilage and Ocimum basilicum gum [18]. These generics should be demonstrated to *in vitro* and *in vivo* quality control studies before being established in the markets. However, Amlodipine's biowaiver conditions are considered as a candidate for a biowaiver through dissolution testing [19-21].

Medicines may undergo a potential change during storage due to temperature or humidity. What's more, surveillance for local pharmaceutical factories and conflicts may also be affected on the drug quality. On the other hand, the third goal, which is reported in Sustainable Development Goals is good health and well-being; hence, it's important to confirm the quality of medicines before distributed to the markets. The presence research aims to analyze five different generic products of oral film-coated tablets of

Amlodipine Besylate tablets 5 mg that are commercially available in Yemeni markets. Two of these are locally manufactured by Yemen pharmaceutical factories, whereas, three Amlodipine tablets are imported from Germany, Hungary, and Egypt. The investigation is devoted to *in vitro* various physiochemical studies of Amlodipine tablets 5 mg through different quality control parameters such as thickness, hardness, disintegration test, dissolution time, and drug content. A comparison was carried out *in vitro* drug release test with chemical content between all selected brands.

MATERIALS AND METHODS

Study area and period

The study was conducted from February to June 2021 at Saba Pharma Pharmaceutical Plant, which is located in Sana'a city, Republic of Yemen.

Techniques

Analytical balance (model: GR-120, AND Weighing, Japan), disintegration tester (ED-2L, Electrolab, India), HPLC (Binary, Jasco, Japan), tablet hardness tester (DH250, THERMONIK, India), dissolution test apparatus (DT-810, Jasco, Japan), pH meter (3520, Jenway, United Kingdom), UV-VIS spectrophotometer (V-730, Jasco, Japan) and ultrasonic cleaner (CSA-10BT, Sapeen, Shanghai).

Reagent

Standard Amlodipine was purchased from Merck (USA). Methanol, hydrochloric acid, acetonitrile, phosphoric acid and triethylamine were purchased from SDFCL (India) and used without further purification.

Sample collection

Table 1 is illustrated the label information of five selected brands of Amlodipine Besylate 5 mg tablets that sold in Yemeni Market.

Table 1: Label information (Country, manufacturing date, expiry date and batch No.) of Amlodipine Besylate 5 mg tablets A-E

Brand code	Country	Manufacturing date	Expiry date	Batch No.
A	Germany	June/2020	June/2022	9uk24849
B	Hungary	September/2019	September/2022	T99630A
C	Egypt	April/2019	April/2023	19104067
D	Yemen	March/2020	March/2022	20288A
E	Yemen	December/2019	December/2022	19353

Methods

United States Pharmacopoeia procedures were used to identify the quality of coated film Amlodipine tablets [22].

Weight variation test

Twenty tablets were randomly picked from each brand and individually weighed by using the electronic balance. The average weight of the tablets was calculated and compared with the individual weights. The weight deviation and the percentage deviation of each tablet were calculated based on Formulas 1 and 2, respectively.

$$\text{Weight deviation} = \text{average weight} \times \text{permissible percentage deviation.} \quad (1)$$

$$\%\ \text{deviation for each tablet} = \frac{(\text{Wttab}) - (\text{Wtavg})}{(\text{Wtavg})} \times 100 \ldots . \quad (2)$$

Where: Wtavg = Average weight of tablets, Wttab = Individual weight of each tablet.

Table 2 illustrates the maximum % difference allowance for tablet weight variation as reports in The United States Pharmacopoeia (USP).

Table 2: The accepted percentage weight deviation for the tablets

Average weight of tablets (mg)	Maximum % difference allowed
130 or less	10 %
130 to 324	7.5 %
More than 324	5 %

Hardness test

Ten tablets were selected randomly from each brand. A tablet hardness tester was utilized for this test and the hardness of each tablet was calculated automatically by measuring the required pressure to break the tablet. The mean hardness and±standard deviation (SD) were calculated.

Thickness

Ten tablets from each brand were taken randomly and the thickness was determined in micrometers.

Disintegration test

Six tablets from each brand were placed in an individual tube and covered by disc. Disintegration USP II puddle tester was performed. Water was added as a disintegration media and the temperature was maintained at temperature 37±2 °C as the apparatus was operated. The assembly was raised and lowered between 29 and 32 cycles per minute. When all the masses were entirely dissolved, the time was recorded by second (s) esteem to complete the disintegration test.

Dissolution test

The dissolution test was performed by using dissolution tester USP apparatus-II (paddle) at the rotation speed of 75 revolution per minute (rpm). The dissolution medium was a buffer solution (0.01 N hydrochloric acid, pH 6.8) and the temperature was kept at 37±0.5 °C. The tablets were immersed in the dissolution media (500 ml) for 30 min (min). Subsequently, the solution was filtered to remove the insoluble solids. Two ml of the filtrated solution was taken and diluted with a buffer solution (98 ml) to make the final volume of 100 ml. Finally, the solution was assayed by Uv-Vis spectrophotometer at λ_{max} 239 nm and the absorbance was recorded. The hydrochloric acid buffer solution was used as a blank. To determine the percentage of drug release, the obtained absorbance was compared with the standard solution absorbance and the drug release % was calculated using Formula 3:

$$\frac{\text{Absorbance of the test solution} \times \text{Concentration of the standard solution}}{\text{Absorbance of the standard solution} \times \text{Concentration of the test solution}} \times 100 \ldots (3)$$

Assay test

The drug content assay was performed according to the procedure that is presented in United States Pharmacopoeia. Ten tablets of Amlodipine Besylate were finely powdered and weighed equivalently to the average weighted tablets. To prepare the buffer solution, 7 ml of trimethylamine was placed into a 1000 ml volumetric flask and complete the volume with water. Adjust the pH to 3 by the addition of phosphoric acid (1 N). The Amlodipine powder was transferred to a 50 ml volumetric flask followed by the addition of 40 ml of mobile phase (Mobile phase was Acetonitrile: Methanol: Buffer solution at the ratio 1.5:3.5:50, respectively). After that, the mixture was subjected to sonication for 10 min, cooled, and the volume was made up to 50 ml by the addition of the mobile phase. Then, the mixture was filtered through 0.45 mm pore size to remove the insoluble materials and the first 3 ml of filtrate was discarded. 5 ml of the clear solution was transferred into 100 ml

volumetric flask and diluted with the mobile phase to volume (concentration = 0.05 g/l). Finally, 50 µl of the sample was injected in High-performance liquid chromatography (HPLC) with the flow rates 1 ml/min. The UV-visible spectrophotometer detector was set at 237 nm. The standard solution was tested three runs by using UV-vis spectrophotometer and the average was calculated. On the other hand, three replicate injections of Amlodipine samples were injected and the % of drug content was assessed by using Formula 4.

$$\frac{\text{Area of the test solution} \times \text{Concentration of the standard solution}}{\text{Area of the standard solution} \times \text{Concentration of the test solution}} \times 100 \ldots (4)$$

RESULTS AND DISCUSSION

The results of physicochemical properties including weight variation, hardness, thickness and disintegration test, % drug release along with % drug content of the selected Amlodipine 5 mg tablets brands A-E are tabulated in tables 3 and 4, respectively.

Weight variation test

The weight variation test (uniformity of weight) gives information about the manufacturing quality, applicable tablets particle size, and the content uniformity of the drug formulation [23]. In terms of average weight, all the studied brands did not deviate from USP specification (±7.5 %). It ranged from-3.8 % to+5.13 % to-1.25 % to+3.25 % (table 3). However, small % SD values are a sign of the high homogeneity of the active ingredient and weight distribution of the Amlodipine tablets, and hence, it provides the desired therapeutic response [24].

Hardness test

The hardness test measures the capability of the tablet to resist mechanical shock in handling, manufacturing, packaging, and shipping [25]. The hardness of five brands of Amlodipine was calculated and found as: 10.59±0.97, 13.21±1.5, 6.68±0.66, 5.06±0.31 and 9.26±1.77 for brands A, B, C, D and E, respectively (table 3). All the hardness results met the USP specification.

Thickness test

The thickness test provides information about the variation between tablets. However, it should be controlled within a±5 % variation of a standard value. According to table 3, the average thickness was ranged between 2.682±0.04 (brand D) to 3.676±0.01 (brand A).

Table 3: Physicochemical results weight variation, hardness, thickness of brands A-E

Brand	Weight deviation %	Hardness[a,b]	Thickness[a,b](mm)
A	-1.25 % to+3.25 %	10.59±0.97	3.676±0.01
B	-1.28 % to+2.23 %	13.21±1.5	3.277±0.02
C	-2.08 % to+2.2 %	6.68±0.66	2.887±0.02
D	-1.5 % to+2.03 %	5.06±0.31	2.682±0.04
E	-3.8 % to+5.13 %	9.26±1.77	3.027±0.09

[a]The results aremean±SD (SD: Standard Deviation), [b]Number of replicated = 10

Disintegration time

Drug release rates can be controlled by the amount of polymers used for surface coating [26]. The disintegration times were determined for all five brands and the results are shown in table 4. Brands A, B, C and E disintegrated in 25 s, 35 s, 41 s, 55 s, respectively, while brand D disintegrated in 2 min: 30 s. Even though all brands are in good agreement with the USP specification (disintegration time should be less than 15 min), there is a significant variation in the results. This variation can be explained in terms of drug formulation (type and quantity of disintegrants). Sodium starch glycolate entity, binders, microcrystalline cellulose, and lubricants that exist in the drug formulations fastens the disintegration, and hence, improves the drug stability [27-29].

Dissolution test

The dissolution test (drug release) is an important test in quality parameters because it reflects the absorption and bioavailability of the drug. It might be affected by the disintegration test [28-31]. According to USP, 75 % of the drug (Q) should be dissolved within 30 min. This value corresponds to gastric emptying half-life (T_{50}%) in fasting conditions [30]. Drugs with poor dissolution profiles will decrease the bioavailability of the drug, thereby leading to therapeutic failure [31, 32]. After 30 min, the drug release of selected Amlodipine brands ranged from 93.7±2.24 % to 98.4±0.85 %. Brand D (98.4±0.85) and brand B (98.3±1.06) showed the highest percentage of drug release of the entire samples. From table 4, it is observed that there is no relation between the disintegration and *in vitro* drug release. Various attempts have been developed to improve the quality of the dissolution and hence bioavailability of drugs [33], enteric coating is one of the strategies performed alone or in combination with other approaches [34, 35].

Assay test

The content uniformity test (assay test) implements to confirm that all tablets contained the active ingredient content of the desired drug [36]. The USP provides the monograph for the determination of Amlodipine in the film-coated tablet using HPLC with an ultraviolet detector. The accepted limit for Amlodipine Besylate is 90 %-110 % with the standard deviation less or equal to 6 %. Table 4 revealed the satisfied contents of the active ingredient as 100.15±0.33, 97.46±0.35, 99.21±0.17, 98,36±0.79 and 93.22±0.38 for brands A, B, C, D and E, respectively. Brand A has the highest content of 100.15 %, whereas brand E shows the lowest content of 93.22 %. Despite the varsity of the drug content among the brand, but values are still in good agreement with the pharmacopeial requirements.

Table 4: Disintegration test, % drug release and % drug content results of brands A-E

Brand	Disintegration time	% Drug release[a,b]	% Drug content[a,c]
A	25 s	93.7±2.24	100.15±0.33
B	35 s	98.3±1.06	97.46±0.35
C	41 s	96.7±0.80	99.21±0.17
D	2:30 min.	98.4±0.85	98.36±0.79
E	55 s	97.9±4.9	93.22±0.38

[a]The results aremean±SD (SD: Standard Deviation), [b]Number of replicated = 6, [c]Number of replicated = 3

CONCLUSION

Several quality control parameters, including weight variation, hardness, thickness, disintegration time, dissolution and assay tests, were conducted to evaluate the quality of five different Amlodipine 5 mg brands that are available in pharmaceutical markets in Yemen. The investigation revealed that the five brands of Amlodipine 5 mg tablets complied with pharmacopoeial limits (USP). No significant

differences were observed in weight variation and thickness. The disintegration time was ranged from 25 s (brand A) to 2:30 (brand D). The dissolution test of all brands was found between 93.7±2.24 and 98.4±0.85%. In this study, the disintegration time did not show a direct relationship with their drug release. The assay results revealed the drug content of the brand was ranged from 93.22±0.38 % to 100.15±0.33 %. In conclusion, the selected local and imported Amlodipine Besylate 5 mg generics are pharmaceutical equivalence and met the quality limit according to USP specifications; therefore, the local Amlodipine Besylate 5 mg can be used safely to get the desired therapeutic efficiency.

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AUTHORS CONTRIBUTIONS

Arwa Alshargabi wrote the manuscript draft and design the concept and finalized the manuscript.

CONFLICT OF INTERESTS

The author confirms they have no conflict of interests.

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