

Comparative *in-vitro* Assessment of Five Amlodipine Tablets Marketed in Tripoli Libya

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Abstract- Amlodipine belongs to a group of medicines called calcium-channel blockers, used to treat high blood pressure [hypertension] or certain type of chest pain (angina), In patients with high blood pressure amlodipine works by relaxing blood vessels, so that blood passes through them more easily, In patients with angina amlodipine works by improving blood supply to the heart muscle which then receives more oxygen and as result chest pain is prevented. The availability of several brands of Amlodipine tablets in Libyan pharmacies today places health practitioners and a pharmacist in a problem of drug substitution in case of a particular brand is not available. The main purpose of this study was to evaluate the pharmaceutical properties of some commercial amlodipine 5mg tablets available in Tripoli Libya. Five different brands of amlodipine tablets were purchased from private pharmacies, with different price ranges, produced by various international pharmaceutical companies. Physicochemical properties of these tablets were assessed using official and unofficial quality control tests prescribed in different Pharmacopoeia included evaluation of appearance observation, hardness, thickness, diameter, friability, Content uniformity, weight variation, disintegration, dissolution as well as identification test by IR was conducted. The entire selected brands complied with the official test as prescribed by the United States Pharmacopoeia standards and British Pharmacopoeia Standards except brand B and E show only 80% and 85% respectively which is less percentage of the labeled amount of amlodipine active ingredient which should be within the acceptable range of 90-110% of the labeled amount. Results of dissolution test are all within the acceptable range of not less than 75% of the labeled amount of dissolved amlodipine. It can be concluded that brand A, C and D could be regarded as bioequivalent and therefore can be interchanged in the clinical practice; this sort of study is good indicator for the evaluation of the idealness of commercial products and showed the importance of post marketing investigation for the drugs imported and distributed in Libya.

Keywords: Amlodipine tablets, Evaluation, Bioequivalence, Quality control, Generic drugs.

1. INTRODUCTION:

Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and major attention of the researcher is towards this direction [1]. Furthermore, oral delivery of drugs is the utmost chosen route of drug delivery due to the ease of administration; low cost of therapy, patient compliance, and flexibility in formulation [2]. Post market medicines monitoring serves as a confidential tool to judge the quality, therapeutic efficacy and safety of medicine [3]. Improvement of existing regulations and product development can be accelerated with the help of information obtained from such monitoring [4]. Many pharmaceutical companies started to manufacture different types of medicine to control the high blood pressure. These products may be branded original and proved by FDA or unbranded generics called a faithful imitation of a mature drug, an exact simulation of an established drug but not approved by a patent, had the same active ingredients and expected to show bioequivalent to the branded drug, and sometimes, fake [5]. 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 [6]. There is rise in the number of generic drug products from various sources and the variable responses of these products may be due to different factors i.e. the raw material used, method of handling and packaging hence, to ensure interchangeability for such formulations, their pharmaceutical and therapeutic equivalents should be determined [3]. If the quality of generic medicines is comparable with the innovator brand and they are bioequivalent, then the chances of therapeutic failure can be reduced [4].

Amlodipine is a white crystalline powder with a molecular formula of (C₂₀H₂₅N₂O₅Cl), its structure is represented in Figure (1), chemically 3-ethyl 5- methyl-2-[(2- aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, with molecular weight of 408.9 g/mol.[7]. Amlodipine belongs to the group of long acting calcium channel blockers used in treatment of chronic angina, vasospastic angina and hypertension [8]. It is slightly soluble in water and sparingly soluble in ethanol. Amlodipine (as besylate, mesylate or maleate) is a long- acting calcium channel blocker (dihydropyridine class) used as an antihypertensive and in the treatment of angina. Like other calcium channel blockers, amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle [9, 10]. Amlodipine is commercially available in tablet dosage form given orally, in once daily doses of 5 and 10 mg as it has a half-life of 30-60 hours [11, 12].

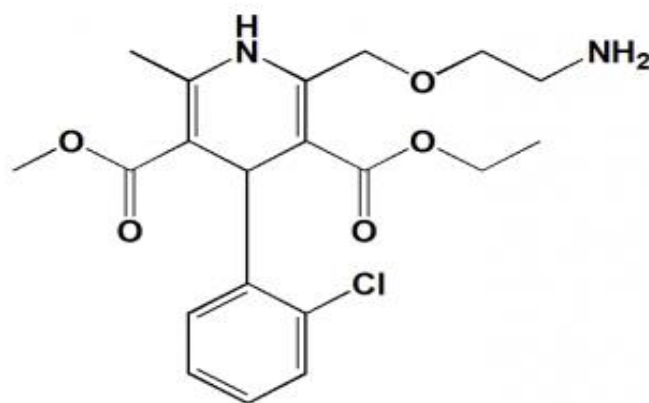


Figure 1: Chemical Structure of Amlodipine

In Libya, there are many different brands of Amlodipine tablets available from different multinational companies. Each brand has its own formulation which affects the release and delivery of drug and produce variable clinical responses. Evaluation of *in-vitro* release and the physicochemical properties of these brands are very important as it can be used to evaluate the bioavailability and pharmaceutical equivalence [13]. Various brands available in the market are considered pharmaceutically equivalent if they contain the same amount of active ingredients in the identical dosage form and meet the same compendia standards in strength, quality, purity and identity but may differ in shape, packaging, excipients, expiration time and labeling requirements [14]. According to World Health Organization (WHO) the prevalence of fake medicines was higher in developing countries with weak regulations, enforcement, and scarcity of supply of essential medicines, unregulated market, and unaffordable prices [15]. For these reasons, the safety, quality, and efficacy of drug products especially in developing countries cannot be granted, therefore post market qualitative studies are important, few drug quality control studies have been conducted so far in Tripoli Libya, these studies encouraged to examine the medicine quality for continuous monitoring and to control drug products in the market that might prevent the prevalence of counterfeits and sub-standard medicines and ensure the use of medicines of standard quality and different brands available are pharmaceutically equivalent [16-20]. Moreover, no such evaluation on Amlodipine besylate of the local market was carried out before. These facts directed our interest to assess the quality of some commercially available Amlodipine besylate tablet in Tripoli market.

2. MATERIALS AND METHODS:

Distilled water, 0.01 hydrochloric acid, KBr, pure sample of Amlodipine obtained from quality center department, randomly five brands of Amlodipine with strength 5mg uncoated tablet was obtained from different private pharmacies. The products were coded as A, B, C, D and E as illustrated in Table 1 all drugs included in the study was within the validity date limit.

Table 1: Label information of five different brands of Amlodipine tablets under investigation

Product code	Batch No.	Manufacture Date	Expire Date	Price/tablet in LYD
A	1279848	9\2018	8\2022	1
B	03389	8\2017	3\2024	0.26
C	A69001	6\2018	6\2022	0.17
D	805113	Not present	12\2022	0.13
E	8920357	3\2020	3\2024	0.4

2.1 Visual Inspection:

Samples of 20 tablets from each batch were selected randomly and inspected for their external characteristics such as color, surface texture and shape, presence of grooves; monograms and coat were described based on the visual observation.

2.2 Weight Uniformity:

Twenty tablets of each product code were weighed using an electronic digital balance, each tablet was weighed individually then the average weight was calculated for each brand. Tablets were examined for their uniformity of weight and the percentage deviation allowed by USP generally $\pm 10\%$ for tablets weighing 130 mg or less, $\pm 7.5\%$ for tablets weighing more than 130 mg to 324 mg and $\pm 5\%$ for tablets weighing more than 324mg [21].

2.3 Friability:

Ten tablets from each brand were weighed and placed into the friability testing apparatus. Tablets were rotated at 25 rpm for 4 minutes. The tablet were removed, dusted and accurately weighed, and then the friability percentage was calculated for each batch, the friability value for the tablets must be less than 1% of the weight of tablets being tested.

2.4 Hardness and tablet dimensions:

Hardness, thickness, and diameter of samples of 20 tablets were determined using tablet combination tester.(Erweka TBH 320 WTD Multi-Check tester, Germany) In the hardness test, pressure was applied on the tablet and the force caused the tablet to break up was recorded. The optimum hardness regarded for coated tablets is 10-20 kg/cm². Tablet thickness and diameter should be controlled within a $\pm 5\%$ of a standard value. [22, 23]

2.5 Disintegration Test:

Samples of six tablets were selected from each brand. Tablets were placed in six tubes of the basket-rack assembly of the disintegration time tester PTZ Auto 1EZ (Pharma test, Germany) and perforated cylindrical plastic discs were put on top surface of each tablet. The assembly was allowed to move up and down in a beaker containing 1 liter of distilled water at $37 \pm 0.5^\circ\text{C}$, as per condition described by USP. The time taken to break each tablet into small particles and pass out through the mesh at the bottom of the tube was recorded. Mean disintegration time was calculated for each one of the brands

2.6 Dissolution Rate Determination:

Dissolution test was carried out by a dissolution apparatus operating at 100 rpm for 30 min, using 0.01N Hydrochloric acid (900 ml) prepared as a dissolution medium, at $37^\circ\text{C} \pm 2^\circ\text{C}$. Six tablets from each brand were placed in a small wire mesh basket fastened to the bottom of the shaft connected to a variable speed motor. Samples were withdrawn at intervals of 5, 10, 15, 20, 25, and 30 min, on each time, samples were diluted at first by withdrawing 5ml and replacing it with 5ml fresh medium in a 25ml capacity flask, then withdrawing from it 1ml and diluting it again by fresh medium in a 25ml capacity flask. Samples were filtered and absorbance measured at 237nm using pure medium as a blank. The percentage of average drug release for each brand was plotted against time.

2.7 Assay of Amlodipine Besylate Tablets:

Accurately weighed about 0.1g of Amlodipine Besylate dissolved in phosphate buffer (pH 6.8) diluted the solution to 100ml with phosphate buffer. Further 5 ml of this solution was diluted to 100ml with phosphate buffer. The resultant solution was scanned for absorption by UV Spectroscopy maxima (λ_{max}) 239nm.

2.8 Identification

The test was done simply by grinding 10 tablets and from the grinded powder about 3mg was taken, added to 300 mg of KBr powder (FTIR background window) then mixed together till homogenous mixture was obtained. The prepared sample pellet (disc) was achieved or obtained by compression all the mixture and finely measured for spectrum.

3. RESULTS AND DISCUSSION:

Five commercial Amlodipine 5 mg tablets (Table 1) were assessed for their pharmaceutical quality according to the described requirements that are stated in the official compendia. The evaluation tests were performed on the samples while in their intended shelf life. The apparent physical characteristics of the samples based on visual inspection were evaluated. They were all found to have an attractive appearance with smooth surface texture, round in shape, with uniform white colors, all are compressed uncoated tablets, odorless, tasteless, and there were no defects in the tablets.

All brands of Amlodipine tablets were consistent in their weight and exhibited uniform geometrical dimension parameters (Table 2). The deviations of the tablets weight from the average were in the permitted limit with a deviation less than $\pm 7.5\%$. Brand A and C exhibited quite similar average weight and all the investigated brands demonstrated similar diameters except brand E that showed to be the smallest in average weight and diameter, Brand A is the most expensive one among the selected brands. The thickness of the brands tested range from 2.45 mm to 4.03 mm. The hardness test results (Table 2), showed that brand A and C exhibited greater capability in resisting chipping, while brand B demonstrated the lowest and weakest solidity in comparison to the other brands. Friability of all tested brands less than 1 % which indicated that comply with the standard pharmacopeia requirement.

Table 2: Evaluated physicochemical parameters of the five brands of Amlodipine tablets

Brands Code	Average weight mg	Dissolution %	Hardness (kg/cm ²)	Disintegration time (min)	Content uniformity (%)	Diameter (mm)	Thickness (mm)	Friability %
A	201.18	98.02	11.01 \pm 0.58	00:03	100%	8.45 \pm 0.02	2.45 \pm 0.02	0.039
B	206.11	98.00	5.70 \pm 0.65	00:03	80%	8.07 \pm 0.04	4.03 \pm 0.06	0.195
C	201.68	93.79	11.70 \pm 0.98	00:02	93%	8.79 \pm 0.05	3.12 \pm 0.02	0.324
D	203.89	96.36	7.03 \pm 1.35	00:02	96%	8.01 \pm 0.06	3.31 \pm 0.01	0.255
E	150.25	96.03	8.74 \pm 1.09	00:05	85%	7.61 \pm 0.04	3.24 \pm 0.03	0.125

The entire brands passed the disintegration time test according to the official limit. Tablets were broken up and disaggregated into their original granules and particles within few seconds. It was found that all brands were in compliance with the standard limit for dissolution test Figure (3). The drug release values were more than 75% in one hour, all the assessed brands exhibited similar patterns of drug dissolution. Brand B and E show only 80% and 85% respectively which is less percentage of the labeled amount of amlodipine active ingredient which should be within the acceptable range of 90-110% of the labeled amount.

Figures (4) to (8) show the IR spectrum of different commercial brands of Amlodipine. It was observed that all spectra obtained for different brands of Amlodipine have similar absorption bands to the IR spectrum of considered standard Amlodipine brand which is brand A. The similarity between the spectra is strongly indicative of the identity of Amlodipine in all of the samples analyzed using IR technique. Our resulted spectrum is completely matched with Amlodipine standard in range of 98 to 99 % for all samples from A to E.

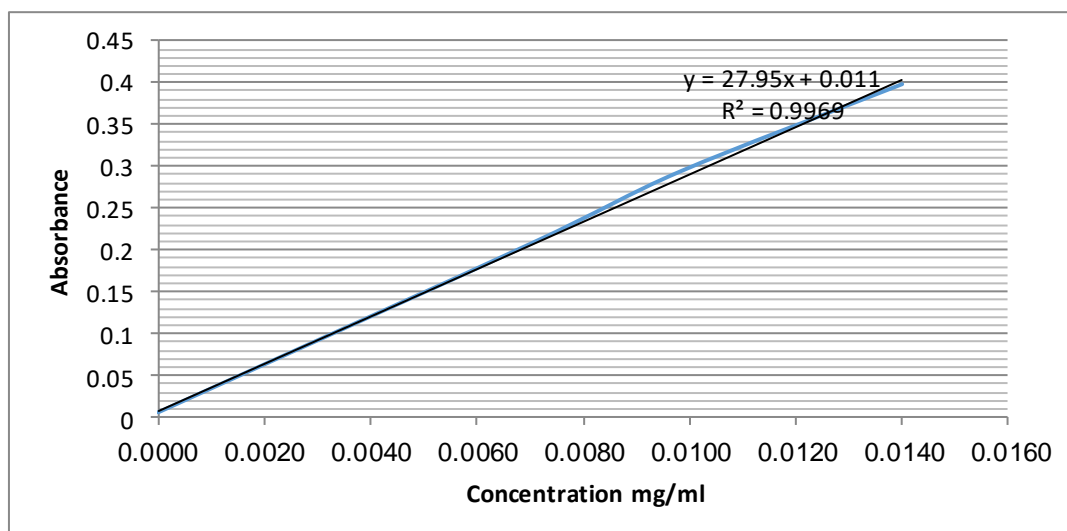


Figure 2: Calibration Curve of Amlodipine

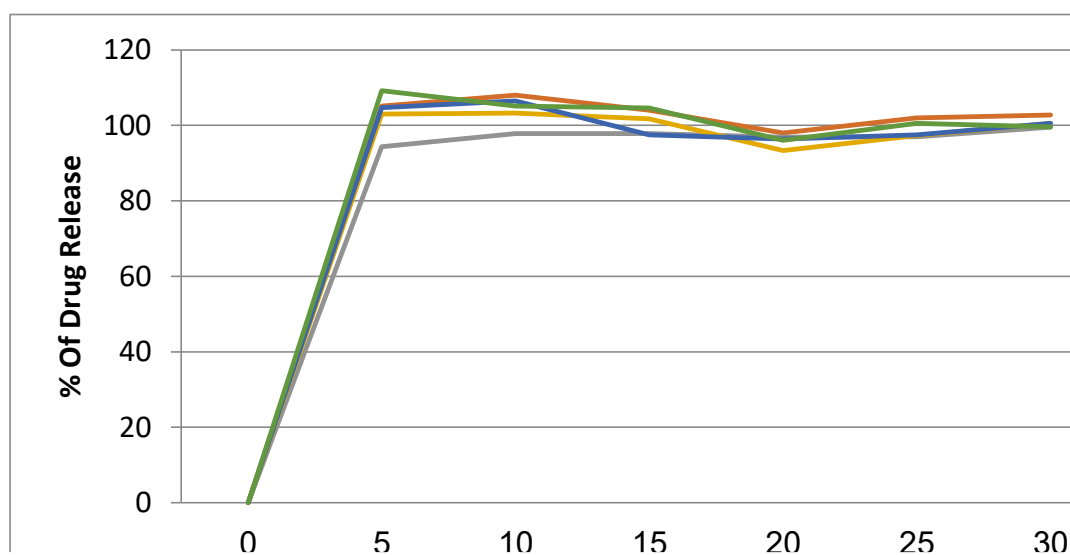


Figure 3: Dissolution curve of different brands of Amlodipine tablets

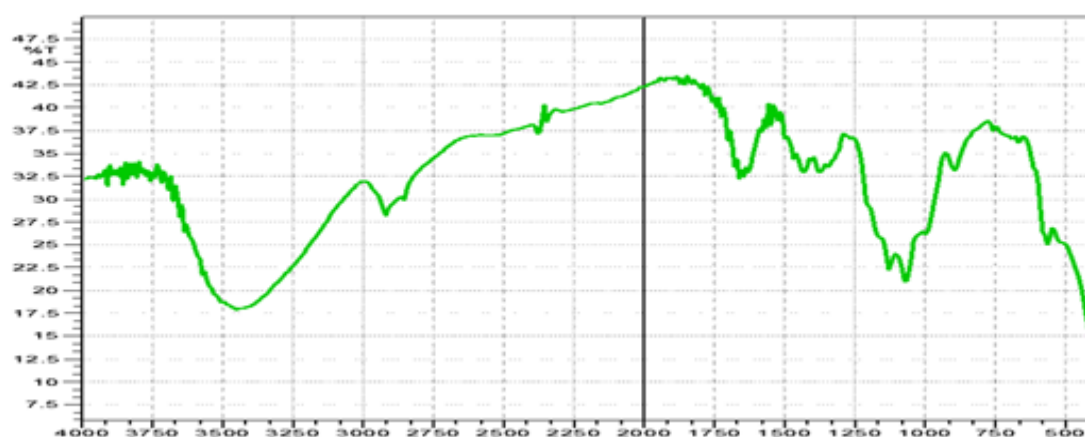


Figure 4: IR spectrum of brand A Amlodipine

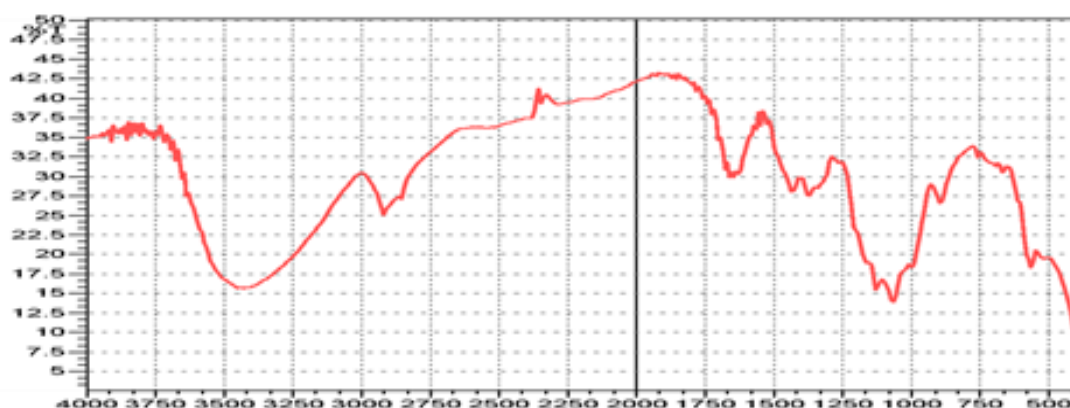


Figure 5: IR spectrum of brand B Amlodipine

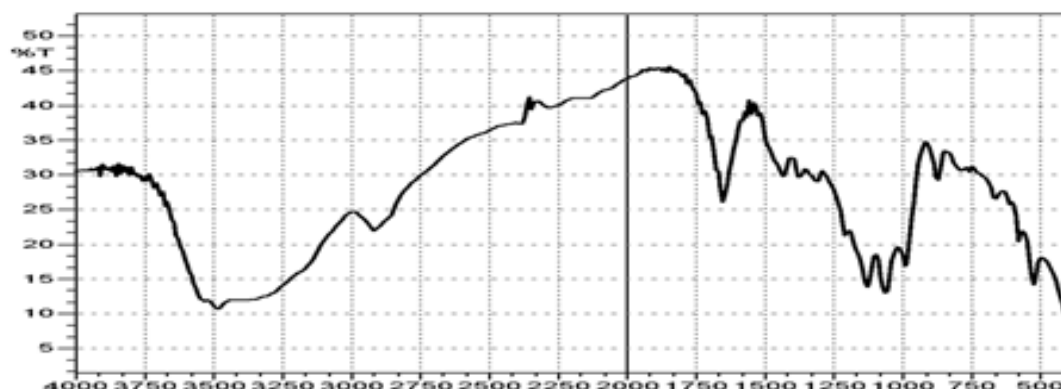


Figure 6: IR spectrum of brand C Amlodipine

CONCLUSION:

It can be concluded that all brands of 5mg Amlodipine tablets available in the local market of Tripoli Libya showed acceptable results, and good overall quality, they were all complied with USP standards, in terms of uniformity of weight, thickness and diameter, they were all within acceptable limits of friability test, hardness and disintegration, as well as all brands displayed excellent dissolution profiles. However, two brands B and E shows less percentage of the labeled amount of amlodipine active ingredient which is out of the pharmacopeia limit. The result founded leading to the conclusion that the other three brands of Amlodipine tablets included in this study (A, C, and D) with variable cost price are pharmaceutically equivalent and could be used interchangeably with the innovator products. This study has also highlighted the need for focusing on the post-marketing evaluation of pharmaceutical products from different manufacturers circulating in the developing countries markets where pharmaceutical products faking, counterfeiting and adulterations are present, to ensure that dosage forms introduced into the market meet the required standards.

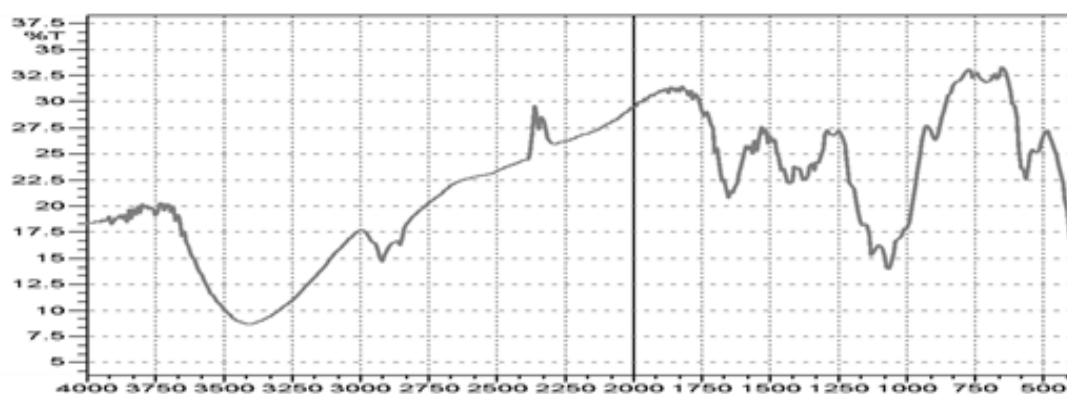


Figure 7: IR spectrum of brand D Amlodipine



Figure 8: IR spectrum of brand E Amlodipine

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