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UofKEJ Vol.5 Issue 1 pp. 26-29 (February -2015)

UNIVERSITY OF KHARTOUM ENGINEERING JOURNAL (UOFKEJ)

A Comparative Pharmaceutical Evaluation of Amlodipine (5mg)

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Abstract: The objective of this study is to evaluate the pharmaceutical properties of three brands of Amlodipine (5mg) for local and international pharmaceutical companies. The main aim is to evaluate whether compliance with the United States Pharmacopeia (USP) is implemented for physical and chemical parameters including: assay, dissolution, hardness, thickness, length and disintegration. A HPLC device was used in the assay test to determine the percentage of the labeled amount of amlodipine (active ingredient) in the portion of tablets or capsules. Results of assay test showed that values for Norvasc, Myodipine and Nordip were 97.83%, 95.31%, and 93.64% respectively, which are within the acceptable range of 90-110% of the labeled amount of amlodipine. UV-Visible Spectrometer was used in dissolution test to measure the percentage of dissolved amlodipine. Results of dissolution test showed that values for Norvasc, Myodipine and Nordip were 99.795%, 99.415% and 96.61 respectively, which are all within the acceptable range of not less than 75% of the labeled amount of dissolved amlodipine. Tablets and capsules were subjected to various physical tests which included hardness, thickness, length and disintegration. Results were statistically analyzed as per USP official methods. The study concluded that all brands of Amlodipine Besylate showed satisfactory results for the chemical and physical tests.

Keywords: *Amlodipine Besylate (5mg); Generic drugs; Bioequivalence; Pharmaceutical equivalent*.

1. INTRODUCTION

The essential drug concept supports the use of generic medicines so as to improve access to essential medicines via drug price control [1]. A generic medicine is defined as an exact simulation of an established drug, not protected by a patent and promoted with the chemical name of the active ingredient [2]. 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, methods 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].

Suitable tests to assess bioequivalence (BE) in cost effective manner are required in many developing countries so as to avoid extensive supply of poor quality and/or counterfeit drug products in a market. Over the past three decades, dissolution test has emerged as a potent tool for characterizing the quality of oral pharmaceutical products. The Biopharmaceutics Classification System (BCS) was introduced in 1995 for bioequivalence testing, in which drugs are classified on the basis of their aqueous solubility and intestinal permeability [5].

Amlodipine ($C_{20}H_{25}N_2O_5Cl$) is a dihydropyridine calcium antagonist which inhibits the trans-membrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It is used to treat hypertension, chronic stable angina, and confirmed or suspected vaso-spastic angina [6]. Chemically, amlodipine is 3-ethyl 5-methyl 2-[(2- aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine-3, 5-dicarboxylate. Fig. 1 illustrates the molecular structure of Amlodipine.

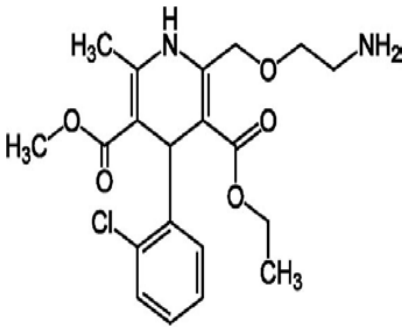

Fig. 1. Molecular Structure of Amlodipine

Amlodipine is illustrated as slightly soluble in water in different Pharmacopoeias [7,8], having experimental water solubility of 75.3 mg/L [9], and the lowest solubility in the pH range from 1 to 6.8 (at 37 °C) is 1 mg/ml [10]. Within the gastrointestinal pH range, Amlodipine is a weak base having pKa of about 8.6 at 25 °C [9]. Amlodipine is scheduled in the WHO Model list of drugs as an antihypertensive agent (5-mg tablet) [11]. The need for continuous pharmaceutical equivalent assessment of multiple brands of clinically useful pharmaceutical products cannot be over emphasized, most especially in developing countries where pharmaceutical products faking, counterfeiting and adulterations are present. It is available in Sudan in 2.5 mg, 5 mg and 10 mg doses and it is widely accepted and used in the management of hypertension.

2. MATERIALS AND METHODS

2.1 Materials

Working standard of Amlodipine Besylate was supplied by Azal Pharmaceutical Industries CO. Ltd. Its purity was reported to be 98.19% according to the company's certificates. Triethylamine, methanol, hydrochloric acid, acetonitrile, phospheric acid all these chemicals were obtained from Azal Pharmaceutical Industries CO. Ltd. Three different brands of commercial Amlodipine Besylate 5 mg were purchased from different local and international retail pharmacies as shown in Table 1.

2.2 Equipments

The equipment used in this study include

- High Performance Liquid Chromatographic (HPLC) YL9100HPLC System, Auto sampler, Serial No 130254, Instrument Code (IC-83), Korea.
- UV-Visible Spectrometer, UV-1800 Shimadzu, Model UV 1800-24 OV, Serial No A1145805715CD, (IC-50), Japan.
- Thermionic disintegration test apparatus, Erweka ZT-2 Husenstamn, Germany
- Dissolution tester (IC-80), India
- Shaker
- Ultrasonic bath.

2.3 Methods

Tablets were subjected to various chemical and physical tests which included assay, dissolution, thickness, length, width, hardness and diameter.

Table 1. Label Information of Three Brands of Amlodipine Besylate (5mg)

Brand	Country	Batch No	Manufacturing date	Expiry date
Norvasc	USA	A335902	04/2013	03/2018
Myodipine	Jordan	32021	08/2013	08/2016
Nordip	Sudan	131	02/2014	02/2016

2.3.1 Assay

The Assay test was conducted according to the method shown in Table 2.

The percentage of the labeled amount of Amlodipine in the portion of tablets or capsules was calculated as follows:

$$\text{Result} = \frac{r_u}{r_s} * \frac{c_s}{c_u} * 100\% \quad (1)$$

$$c_s = \left(\frac{w_s}{v_s}\right)\left(\frac{P}{100}\right)\left(100 - \frac{w_c}{100}\right)\left(\frac{M_{r1}}{M_{r2}}\right) \quad (2)$$

$$c_u = \left(\frac{w_u}{v_u}\right)\left(\frac{L}{\text{average of } 20 \frac{\text{tablets}}{\text{capsules}}}\right) D \quad (3)$$

$$Q\%, \text{assay} = \left(\frac{r_u}{r_s}\right)\left(\left(\frac{w_s}{v_s}\right)\left(\frac{P}{100}\right)\left(100 - \frac{w_c}{100}\right)\left(\frac{M_{r1}}{M_{r2}}\right) D\right)\left(\left(\frac{v_u}{w_u}\right) * \left(\text{average of 20 tablets or} \frac{\text{capsules}}{L}\right) * \left(\frac{1}{D}\right)\right) * 100\% \quad (4)$$

Table 2. Method of Assay

Buffer	Add 14 ml of triethylamine into a 2000 ml flask containing 1800 ml of water. Adjust the solution with phosphoric acid to a pH of 3.0 ± 0.1. Dilute with water to volume and mix well
Mobile phase	Methanol, acetonitrile, and Buffer (1400:600:2000)
Standard solution	Weight 20mg from working standard into 100 ml flask and dilute in mobile phase to volume. Put in wise clean (Ultrasonic cleaner) pass the solution under filter of 0.45- pore size -µm. Take 5 ml from standard solution using a pipette and drain it in a conical flask of capacity 50 ml and inject into HPLC
Sample Stock Solution	Place 5 Tablets or capsules into a 250 ml volumetric flask. Add 25 ml of Mobile phase to the flask, and swirl to disintegrate the tablets or capsules. Add 150 ml of Mobile phase, insert the stopper into the flask, and shake on a reciprocating shaker for 30 min. Dilute with Mobile phase to volume and mix well.
Sample Solution	Take 10 ml from sample stock solution using a pipette and drain it in a conical flask of capacity 50 ml. Pass the sample through a syringe tip filter of 0.45µm pore size.

where:
r_u = peak response from the Sample solution
r_s = peak response from the Standard solution
C_s = concentration of USP Amlodipine Besylate RS in (mg/ml)
C_u = nominal concentration of Amlodipine in the sample solution (mg/ml)
L = label claim (mg/tablet or capsule)
D = dilution factor of the sample solution
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.06
Vs = volume of the sample solution
P = Potency, 98.19%
Wc = water content, 0.1
W_s = weight of the standard solution

2.3.2 Dissolution

The dissolution test was conducted as shown in Table 3. The amount of amlodipine dissolved was determined by using UV absorption at the wavelength of maximum absorbance at about 239 nm on portions of the sample solution in comparison with the Standard solution, using a 1-cm quartz cell and the medium as blank.

Calculate the percentage of the labeled amount of amlodipine dissolved:

$$\text{Result} = \left(\frac{A_U}{A_s}\right)\left(\frac{C_s}{L}\right) D \left(\frac{M_{r1}}{M_{r2}}\right) 100V \qquad (5)$$

$$Cs = \left(\frac{W_s}{V_s}\right)\left(\frac{P}{100}\right)\left(100 - \frac{w_c}{100}\right) \qquad (6)$$

where:
A_u = absorbance of the sample solution
A_s = absorbance of the standard solution
C_s = concentration of the standard solution (mg/ml)
L = label claim (mg/Tablet), 5 mg
D = dilution factor of the sample solution
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.06
V = volume of Medium, 500 ml

2.3.3 Disintegration Test

It was carried out by using Thermionic disintegration test apparatus. To test for Disintegration time, one tablet was placed in each tube and disintegration test was carried out in distilled water at 37 ± 2°C. The time when all the 6 tablets disintegrated and all the particles passed through 10 mesh (wire mesh) was recorded as the 'Disintegration Time' of the tablets or capsules.

Table 3. Method of dissolution

Medium	0.01 N hydrochloric acid; 500 mL
Apparatus	75 rpm. (Use paddles covered with Teflon or made of any inert material except stainless steel.)
Time	30 min
Standard solution	Weight 0.0140 g from working standard into 100 ml conical flask, and dilute in medium to volume. Take 5 ml from standard solution using a pipette and drained it in a conical flask of capacity 50 ml, dilute with medium to volume.
Sample solution	Pass a portion of the standard solution under test through a suitable filter of 0.45 □ m pore size.

2.3.4 Hardness, Thickness and Diameter Test

Take 10 tablets randomly and place them between two platens (jaws), one of which is attached to a load cell and the other to a motor which provides the mechanical drive. During testing, the motorized jaw drives forward pressing the tablet against the fixed jaw until such time as the tablet breaks whereupon the motorized jaw retracts and the load required to break the tablet is recorded.

2.3.5 Dimension Test

Take 10 capsules randomly and take average dimensions for length and width.

3. RESULTS AND DISCUSSION

The results for the physical and chemical analysis are shown in Table 4. Results were statistically analyzed as per USP within the acceptable range. According to USP, Amlodipine Dissolution (Q%) should not be less than 75% of the labeled amount. Results show values of 99.795% for Norvasc, 99.415% for Myodipine and 96.61% for Nordip, which are all within the acceptable range. Disintegration time of Amolodipine Besylate was found to be in the range of 12 min.

Table 4. Physical and chemical analysis of brands

Test	Nordip (tablets)	Myodipine (capsules)	Norvasc (capsules)
ASSAY %	93.64	95.31	97.83
RSD %	0.09	0.21	0.22
Q%	96.61	99.415	99.795
Length (mm)	-	15.754	15.667
Width (mm)	-	5.677	5.617
Thickness (mm)	4.332	-	-
Hardness ()	10.824	-	-
Diameter (mm)	8.07	-	-

4. CONCLUSSIONS

It can be concluded that all brands of Amlodipine Besylate showed acceptable results for the chemical and physical tests including assay, dissolution, hardness, thickness, length and disintegration. They were all compliant with the United States Pharmacopeia (USP).

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