WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 9, 118-126 Research Article ISSN 2278 – 4357

ASSESSMENT OF PHARMACEUTICAL QUALITY CONTROL AND BIOEQUIVALENCE OF VARIOUS BRANDS OF AMLODIPINE BESYLATE 10 MG TABLETS MARKETED IN SUDAN UNDER BIOWAIVER CONDITIONS

Manal AL-Yosofy*[1] and Yasser AL-Domini[2]

*[1]University of Medical Sciences and Technology Sudan.

[2]Production Manager, Azal Pharmaceutical Co. Ltd, Khartoum North Industrial Area –Sudan.

Article Received on
02 July 2018,

Revised on 22 July 2018,
Accepted on 11 August 2018

DOI: 10.20959/wjpps20189-12213

***Corresponding Author**
Manal AL-Yosofy
University of Medical Sciences and Technology Sudan.

ABSTRACT

The aim of this study was to evaluate and compare two different Amlodipine Besylate 10 mg tablets brands commercially available in the Sudanese market with the Innovator. Amlodipine Besylate, a calcium channel blocker, is classified as BCS Class I and may be evaluated under biowaiver conditions. The pharmaceutical equivalence of two Amlodipine Besylate 10 mg tablets was evaluated using official and non-official standards according to USP37-2014 including weight variation, diameter, hardness, disintegration, friability, thickness, assay and dissolution rate. Dissolution profiles were studied using three different buffer solutions: pH 1.2, 4.5, and 6.8 and evaluated using the similarity factor f2 to predict the likely in vivo bioavailability and bioequivalence. All the tested three brands were complied with the official requirements according to USP37-2014. The dissolution profiles of brand A, B and Innovator in pH 1.2, 4.5 and brand A in pH 6.8 were found to be very rapidly dissolving (≥ 85% release in 15 minutes), while the brand B and Innovator in pH 6.8 could not fulfill biowaiver requirements. so they could not pass the WHO criteria ((≥ 85% release in 15 minutes). Similarity factor (f2) and difference factor (f1) were used to assess bioequivalency among the brand B and innovator in pH 6.8. For the brand B and innovator in pH 6.8 the similarity factor f2 value was 53 and difference factor f1 was 7. These results indicated that all generic Amlodipine Besylate tablets included in this investigation were bioequivalent with the chosen innovator brand and so may be used interchangeably.

KEYWORDS: Biowaiver, Amlodipine Besylate, Tablet, Dissolution profiles, Similarity factor.

INTRODUCTION

Amlodipine is a long-acting 1, 4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, amlodipine prevents calcium-dependent myocyte contraction and vasoconstriction. A second proposed mechanism for the drug's vasodilatory effects involves pH-dependent inhibition of calcium influx via inhibition of smooth muscle carbonic anhydrase.[1] Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate, monobenzenesulphonate.[2]

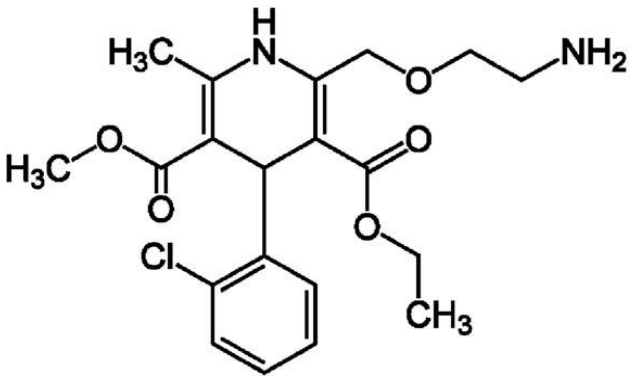

Figure 1: Structure of amlodipine.

Amlodipine besylate is a white crystalline powder. It is slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate tablets are formulated as white tablets equivalent to 2.5, 5, and 10 mg of amlodipine for oral administration.[3]

Hypertension is the third leading killer in the world. There are one billion hypertensive globally, and four million people die annually as a direct result of hypertension. In the Eastern Mediterranean Region, the prevalence of hypertension averages 26% and it affects approximately 125 million individual.[4] Hypertension has the highest prevalence among the major NCDs in Sudan (prevalence of 23.6 in Khartoum state). Hypertension accounts for 1.3% of the outpatient visits it is represented as one of the 10 leading disease treated in health facilities (outpatients) and also one of the 10 leading causes of the deaths in Sudan.[4,5]

A biowaiver has been regarded as an official approval of the waiver for conducting a bioequivalence study in the context of an application for drug approval process.[6]

Biowaiver was adopted by the, Food and Drug Administration (US-FDA), World Health Organization (WHO) and European Medicines Agency(EMA) for implementation in the approval of some generic drug products 6,7,8 to streamline the introduction of the generic drug products and even further reduce the prices in the market place while still assuring (very good) drug product performance.[7,10]

Amlodipine besylate is listed in WHO Model List of Essential Medicines. According to WHO Technical Report, Amlodipine besylate in vitro equivalence may be evaluated under Biowaiver conditions for BCS Class I.[10]

MATERIALS AND METHODS

The tablets tested were immediate release dosage forms of Amlodipine besylate 10mg. Two generic brands of Amlodipine besylate 10mg tablets (Brand A and Brand B) they were selected based on one factory locally and the other imported as test samples and purchased from registered pharmacy and innovative brand (Norvasc® 10mg) was used as the reference sample.

Active content of generic and innovator brands were assessed using the US Pharmacopeia 2014 method.[2]

Table 1 Show brands of Amlodipine besylate tablet, their manufacturing and expiry date.

Table 1: Amlodipine Besylate Tablet Brands.

Name of drug	Batch NO.	Mfg.	Exp.
Innovator	6157	07/2016	06/2019
Brand A	7093	03/2017	03/2019
Brand B	G601687	05/2016	04/2018

Table 2: Physicochemical Properties of 3 Different Brands of Amlodipine Besylate Tablets.

Item	Weight Variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (KP)	Disintegration (min)	Friability (%)	Assay (%)
Innovator	400.0	10.536	4.384	12.81	0:43	0.01	98.28
Brand A	192.9	8.646	3.254	10.81	2:14	0.01	98.28
Brand B	91.5	5.678	2.532	9.71	11:19	0.02	97.45

Reagents

Reagents used were of the analytical grade, Hydrochloric acid, Monobasic potassium Phosphate, Sodium acetate trihydrate, Acetic acid solution, Methanol, Acetonitrile and Triethlamine(SDFCL, India), Potassium chloride (CDH, India), Sodium Hydroxide and Phosphoric Acid (Scharlau, Spain), Reference Amlodipine besylate powder (working standard).

All of these substances were a gift sample from Azal pharmaceutical Co. Ltd. Sudan.

Instruments: Analysis of Amlodipine besylate was carried out on UV -Vis Spectrophotometer (shimadzu UV-1800, Japan), Dissolution tester (Pharma test D-63512, Germany), Electronic balance (Sartorius ED2245, Germany), pH meter (Sartorius pp-20, Germany), Friability tester (Pharma test PTF 20 E, Germany) Disintegration tester (Electrolab ED2SAP0, India), and Hardness tester (Pharma test PT B511F, Germany).

Dissolution study: The dissolution profile of Amlodipine besylate tablets was assessed in 900ml of buffer pH 1.2, 4.5 and 6.8 using US Pharmacopoeia dissolution apparatus II at 75rpm. 500 ml 0.1 N hydrochloric acid pH 1.2, maintained at 37±0.5C, was used as dissolution medium. Same procedure as mentioned above was followed for, acetate buffer of pH 4.5 and phosphate buffer of pH 6.8 USP. In all experiments, 5mL sample aliquots were withdrawn at 10, 15, 20, 30, 45 and 60 min using syringe and immediately replaced with equal volumes of fresh medium at the same temperature to maintain constant total volume during the test.[10] All samples were filtered to remove any insoluble excipient. Twelve tablets per brand were used for the study. Drug release was assayed spectrophotometrically.

Data analysis: Dissolution profiles were evaluated by using Similarity factor, similarity factor f2 as described by the US FDA and presented in the following equation:

$$f2 = 50 \cdot \log \{[1 + (1/n)\Sigma t=1n (Rt - Tt)2]-0.5 \cdot 100\}$$

The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent of dissolution between the two curves. Where n is the number of time points, Rt is the dissolution value of the reference batch at time t, and Tt is the dissolution value of the test batch at time t. Two dissolution profiles are considered similar when the f2 value is ≥ 50.[11,13]

Difference factor (f1): Difference factor can be mathematically computed by using:

f1= {[t+1 n |Rt-Tt|]/ [t+1nRt]} *100

The difference factor (f1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves.[11,13]

RESULTS

Table 3: Dissolution Amount (Rapidly Dissolving, Very Rapidly Dissolving, Or Not Rapidly Dissolving) for Evaluated Drugs.

Medium	Item	% Dissolved(*x*) 15 min	% Dissolved(*x*) 30 min
pH 1.2	Innovator	101.43	101.43
	Brand A	102.08	100.49
	Brand B	98.11	98.44
pH 4.5	Innovator	99.43	100.29
	Brand A	98.79	99.63
	Brand B	95.27	96.91
pH 6.8	Innovator	79.70	86.34
	Brand A	96.28	96.27
	Brand B	72.45	85.50

Table 4: Dissolution Test Results for Amlodipine Besylate 10 Mg Tablets.

Medium	Time (min)	Innovator % Dissolved(*x*)	RSD %	Brand A % Dissolved(*x*)	RSD %	Brand B % Dissolved(x)	RSD %
pH 1.2	**10**	98.07	3.09	100.20	4.65	91.90	6.94
	15	**101.43**	2.07	**102.08**	5.32	98.11	2.90
	20	101.80	1.50	101.36	4.85	99.09	2.12
	30	101.43	1.31	100.49	5.11	98.44	1.51
	45	101.48	1.10	101.04	4.86	98.23	1.77
	60	101.77	1.05	98.90	5.38	97.96	1.63
	F2						
	F1						
pH 4.5	**10**	93.87	8.71	89.20	10.89	89.57	6.40
	15	**99.43**	1.88	**98.79**	3.38	**95.27**	4.52
	20	99.39	1.71	99.83	3.23	96.43	4.35
	30	100.29	1.87	99.63	3.56	96.91	3.53
	45	100.39	1.91	99.23	2.58	96.83	3.42
	60	100.23	2.00	100.41	1.95	96.29	2.90
	F2						
	F1						
pH 6.8	**10**	73.02	5.27	83.80	7.83	53.45	35.81
	15	**79.70**	2.63	**96.28**	3.35	**72.45**	10.00
	20	82.68	3.13	95.80	5.23	77.95	8.02
	30	86.34	2.64	96.27	6.65	85.50	6.52
	45	91.00	1.81	94.51	5.58	90.06	4.78
	60	93.33	2.77	96.01	3.60	91.82	5.00
	F2					**53**	
	F1					**7**	

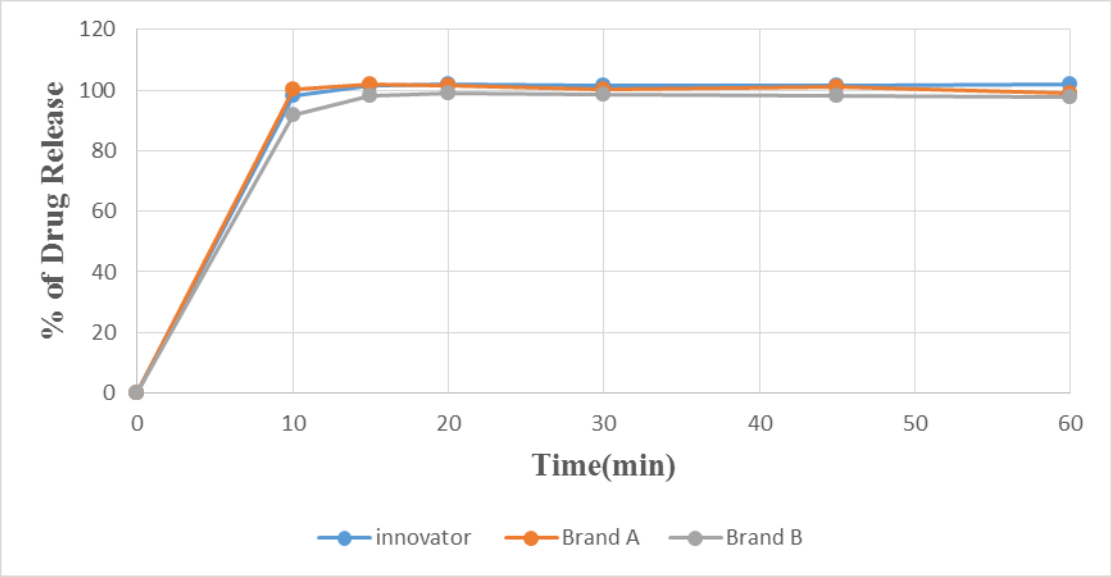

Figure 1: Dissolution Profiles of Tests and Innovator at Ph 1.2 Dissolution Medium.

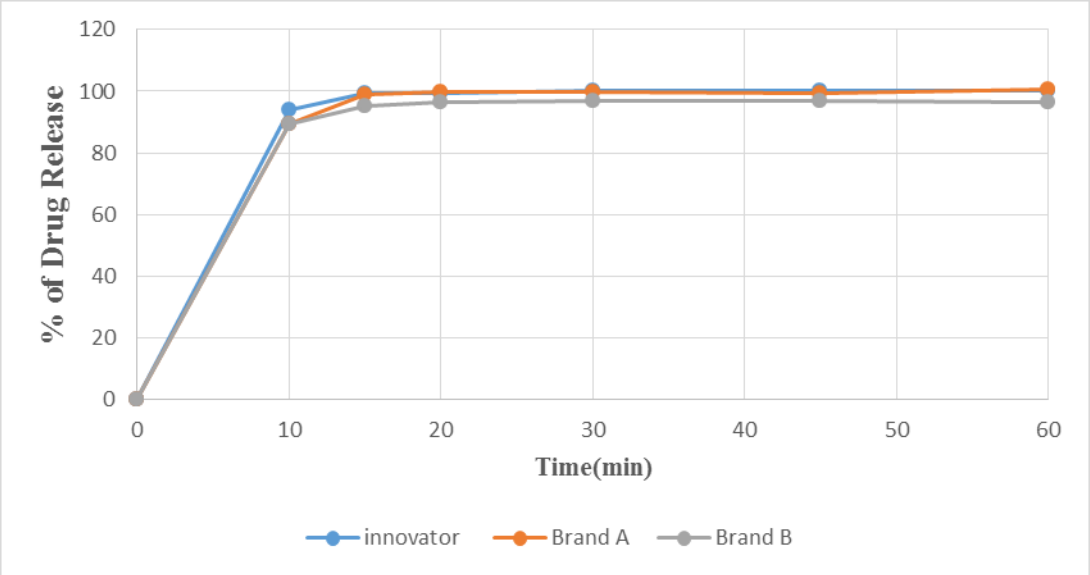

Figure 2: Dissolution Profiles of Tests and Innovator at Ph 4.5 Dissolution Medium.

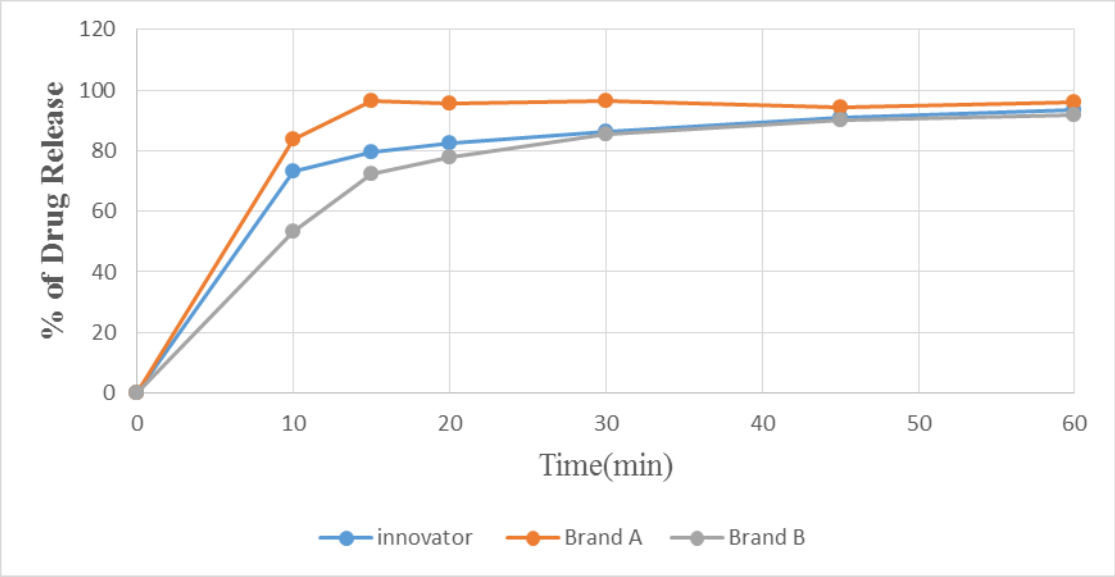

Figure 3: Dissolution Profiles of Tests and Innovator at Ph 6.8 Dissolution Medium.

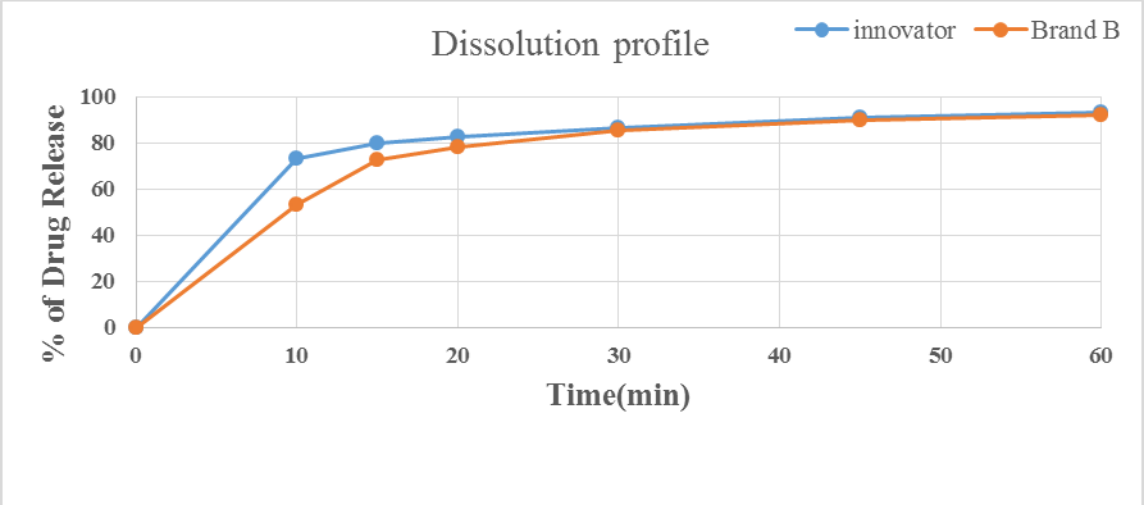

Figure 4: Dissolution Profiles of Brand B with the Innovator at Ph 6.8 Dissolution Medium.

DISCUSSION

The aim of this study was to collect information on the safety, efficacy and possible interchangeability of the different generic Amlodipine Besylate tablet brands with the Innovator by using simple and cost effective in vitro dissolution method. For the purpose of the study, two generic Amlodipine Besylate tablet brands were randomly selected and collected from the market, and their physicochemical properties and release profiles compared with the innovator. All the brands studied complied with the specification for weight variation, diameter, thickness, hardness, and assay.

The test was carried out in three different mediums (pH 1.2, 4.5, and 6.8) to cover the whole GIT environment of different pH **(Table 4)** and **(Fig. 1, 2, 3 and 4)**. Brand A showed very rapid dissolution in all mediums (pH 1.2, 4.5 and 6.8) within 15 minutes **(Table 4)**. Brand B showed very rapid dissolution in mediums (pH 1.2 and 4.5) within 15 minutes but in the (pH 6.8) did not show very rapid dissolution, **(Table 4)**.

Innovator and brand B in pH 6.8 could not fulfill biowaiver requirements. so they could not pass the WHO criteria (($\geq$ 85% release in 15 minutes) **(Table 4).** Similarity factor (f2) and difference factor (f1) were used to assess bioequivalency among the innovator and brand B in pH 6.8. For the innovator and brand B in pH 6.8 the similarity factor f2 value was 53 and difference factor f1 was 7 **(Table 4) (Fig.4)**.

Therefore, dissolution profiles of the test product are similar to those of the innovator product at (pH 1.2, 4.5, and 6.8).

ACKNOWLEDGEMENTS

The authors wish to thank Azal Pharmaceutical co. Ltd for providing material and labs instrument for this study purpose.

REFERENCES

1. drugbank, *Amlodipine.* https://www.drugbank.ca/drugs/DB00381, 2017.
2. Pharmacopeia, U., *United States Pharmacopeia and National Formulary (USP 37–NF 32).* 2014.
3. dailymed, *NORVASC- amlodipine bes ylate tablet Pfizer Laboratories Div Pfizer Inc.* https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=abd6a2ca-40c2-485c-bc53-db1c652505ed&audience=consumer, 2016.
4. Ahmed Ali Sulima, F., Muna Hussein Aboud, M.Med, *Sudan Hypertension Guideline.* www.pascar.org/uploads/files/Sudan_-_Hypertension_Guidelines.pdf, 2012.
5. Omar, S.M., et al., *Assessment of blood pressure control in adult hypertensive patients in eastern Sudan.* BMC cardiovascular disorders, 2018; 18(1): p. 26.
6. Abilash, N. and R. Chandramouli, *Biowaivers-an updated review*. Journal of Pharmaceutical Research, 2017; 16(3): 278-281.
7. Abdelkarim, A., A. Mohammed, and M. Abdeen, *ASSESSMENT OF PHARMACEUTICAL QUALITY CONTROL AND IN VITRO EQUIVALENCE OF VARIOUS BRANDS OF ATENOLOL (100MG) TABLETS AVAILABLE IN SUDANESE*

MARKET UNDER BIOWAIVER CONDITIONS. International Journal of Pharmaceutical Sciences and Research, 2015; 6(6): 2390.

8. Food and D. Administration, *Guidance for Industry. Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system.* https://www.fda.gov/downloads/Drugs/Guidances/ucm070246.pdf, 2017.
9. Agency, E.M., *Guideline on the investigation of bioequivalence.* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf, 2010.
10. Organization, W.H., *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms Technical Report Series, No. 937.* http://www.who.int/medicines/areas/quality_safety/quality_assurance/ProposalWaiveVivoBioequivalenceRequirementsModelListEssentialMedicinesImmediateReleaseSolidOralDosageFormsTRS937Annex8.pdf, 2006.
11. Dressman, J.B., et al., *Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms.* Pharmaceutical research, 2005; 15(1): 11-22.
12. dissolutiontech, *Dissolution Profile Comparison Using Similarity Factor, f2.* http://www.dissolutiontech.com/DTresour/899Art/DissProfile.html.
13. Organization, W.H., *Similarity_factors_f2_f1test.* http://www.who.int/prequal/trainingresources/pq_pres/workshop_Russia/Similarity_factors_f2_f1.xls.