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Research Article

ASSESSMENT OF PHARMACEUTICAL QUALITY CONTROL AND EQUIVALENCE OF VARIOUS BRANDS OF AMLODIPINE BESYLATE (5 MG) TABLETS AVAILABLE IN THE PAKISTANI MARKET UNDER BIOWAIVER CONDITIONS

MAHWISH FEROZ[1], NIGHAT RAZVI[1], SANA GHAYAS[2], FAKHSHEENA ANJUM[2]*, LUBNA GHAZAL[1], SAEED AHMAD SIDDIQUI[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, Pakistan,[2]Dow College of Pharmacy, Dow University of Health Sciences, Karachi, Pakistan. Email: fakhsheena.anjum@duhs.edu.pk

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ABSTRACT

Objective: The study objective was to assess the quality control tests of Amlodipine Besylate generics to assure pharmaceutical and therapeutic equivalence.

Method: Six different brands of Amlodipine Besylate tablets (5 mg tablets), collected from different retail pharmacies in the local market of Pakistan, were characterized through physical and chemical parameters such as, weight variation, hardness, thickness, length, breadth, friability, disintegration, dissolution and assay. The chemical assay of the drug was carried out using a validated UV spectrophotometric method. The dissolution profiles of Amlodipine Besylate tablets under biowaiver condition were evaluated in four different media (distill water, buffer pH 1.2, buffer pH 4.5 and buffer 6.8) using US Pharmacopoeia dissolution apparatus II. Among them dissolution either single point or multiple point including release profile comparison is the most important tool.

Results: Quality control tests were satisfactory and within the limits for all Amlodipine Besylate brands. The results obtained for disintegration test, assay, hardness and friability were less than 15 minutes, 98.96-100.76 %, 1.53-8.77 kg/cm2 and less than 1% respectively. The physico-chemical characteristics of the five generic brands tested were comparable with the innovator brand. They were all within the BP limits as specified for immediate release dosage forms; these assure pharmaceutical equivalence of generics tested with the innovator. The evaluated drugs were "very rapidly dissolving" because the active pharmaceutical ingredient release at time point 15 min was more than 85% so no statistical treatment is required hence are considered to be in- vitro equivalent without in -vivo evaluation. The percent relative standard deviation (% RSD) for all time points fulfills all requirements (≤20% for 15 min, ≤10% for other time points), so results are valid. Under the biowaiver conditions, all the generics are interchangeable with the innovator; they are therapeutically equivalent. The generic substitutions for the innovator are appropriate despite the high price differential.

Conclusion: Product quality is the key issue for selection between generics, but how quality is assessed by pharmacists or other health practitioners is not very clear. Price differential between generics does not necessarily mean poor quality for the cheaper brand. It is obvious from the study that all brands of Amlodipine Besylate tablets are showing satisfactory results for the tests employed and are pharmaceutical equivalent, hence, so as to have cost effective therapy, cheaper brands should be prescribed / suggested by the doctors / pharmacists. In order to make objective decision about generic product selection, pharmacists and other health practitioners need adequate information on suitability of generic for substitution which should be provided by national regulatory bodies after pharmaceutical quality control evaluation of various brands of the drugs available in the market.

Keywords: Bioequivalence, Quality control, Biowaiver, Amlodipine Besylate, Generic drugs.

INTRODUCTION

Amlodipine 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 [1]. Chemically, amlodipine is 3-ethyl 5-methyl 2-[(2- aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine-3, 5-dicarboxylate (Figure 1).

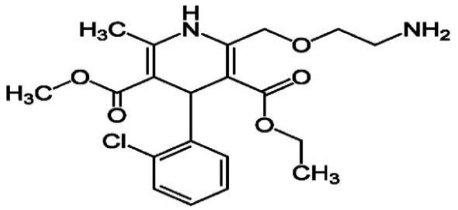

Fig. 1: Structure of Amlodipine

The essential drug concept supports the use of generic medicines so as to improve access to essential medicines via drug price control [2]. 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 [3]. There is raise 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, packaging, etc.

Hence, to ensure interchangeability for such formulations, their pharmaceutical and therapeutic equivalents should be determined [4]. 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 [5]. The price differential between generic and innovator drugs are seldom comparable [6] otherwise large difference exists between the prices of generics available in a market which imposes an impression in general that less expensive drugs are low-grade and less effective [7]. 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 [8]. The studies used to commend comparative in vitro dissolution profile similarity other than the in vivo equivalence testing for test and reference products are called "biowaiver" studies [8, 9]. Biowaivers were established for BCS Class 1 drugs by WHO [9] and FDA [10]. The drugs in Class 1 are rapidly dissolving with

high solubility and high permeability and (bioavailability) BA/BE studies appear redundant for such products [11]. FDA allows Biowaiver for class one drugs and such products can be compared through in vitro dissolution profile similarity with a comparator product [12]. In a study conducted by Somnath et al. (2010),

Ofloxacin was found to show drug release more than 85% within 30 minutes; the product was rapidly dissolving within the BCS limits [13]. Some polymer complexes show higher dissolution rates than the pure drug due to improved aqueous solubility and can be moved from class IV or III to class I [14].

Amlodipine is illustrated as slightly soluble in water in different Pharmacopoeias [15, 16], having experimental water solubility of 75.3 mg/L [17] and the lowest solubility in the pH range from 1 to 6.8 (at 37 °C) is 1 mg/ml [9]. Within the gastrointestinal pH range, Amlodipine is a weak base having pKa of about 8.6 at 25 °C [17]. Amlodipine is scheduled in the WHO Model list of drugs as an antihypertensive agent (5-mg tablet) [18]. Russia has Marketing Authorizations for amlodipine as an immediate-release dosage form in strengths of 2.5, 5, and 10 mg [19]. Thus, the D/S (dose/solubility) ratio for the amlodipine WHO Model List of Essential Medicines dose (5 mg) at a pH range of 1.2–6.8 is 5 mL and 10 mL for the highest dose marketed in Russia. Therefore according to WHO Guidance, amlodipine is a "highly soluble" drug (D/S ratio ≤ 250 mL). Amlodipine's absolute bioavailability is 60–65%, but its permeability is classified as "high" due to metabolite excretion in urine (90–95%). Hence, taking amlodipine's solubility and permeability into account, WHO assigns amlodipine to BCS Class I and its in vitro equivalence can be evaluated under biowaiver conditions for BCS Class I [9]. In this study, the chemical and pharmaceutical equivalence of five different brands of Amlodipine Besylate (5 mg) tablets were investigated which were collected from different retail pharmacies from the local market of Pakistan. Physical and chemical tests were also performed for all the brands which included weight variation, hardness, thickness, length, breadth, friability, disintegration, dissolution and assay. The dissolution profiles of five generics of BCS class I drug (Amlodipine Besylate) with innovator Amlodipine Besylate under biowaiver conditions was also performed. A comparison was also made for lowest priced and highest priced generics with the innovator brand that were selected from the local market of Pakistan.

MATERIALS AND METHODS

In this study, six different brands of commercial Amlodipine Besylate 5 mg tablets were were purchased from different local retail pharmacies and coded as A, B, C, D, E and F. Among them brand A (brand leader) was considered as reference drug because it showed best results for the physico- chemical tests.

Cost Comparison of various Amlodipine besylate (5 mg) brands

The cost comparison of all different brands of Amlodipine besylate was done by the following formula [20]:

(Price of innovator - price of test) ÷ Price of innovator × 100

Physical tests

Tablets were subjected to various physical tests which included weight variation (Mettler Toledo B204-S, Switzerland), thickness, length and breadth (Seiko Brand, 0-150 mm, China), hardness (OSK Fujiwara Hardness Tester, Tokyo, Japan) and friability. The disintegration test was carried out by using Erweka ZT-2 Husenstamn, Germany for which six tablets of each brand were subjected to 900 ml of distilled water that was maintained at 37 ± 2 °C. Results were statistically analyzed as per USP official methods.

Assay for Amlodipine Besylate (5 mg) Tablets

Randomly selected 20 tablets from each brand were weighed and then powdered. A quantity equivalent to 5mg of Amlodipine Besylate was weighed, dissolved in methanol and filtered. The volume of the filtrate was made up to 100 ml using water. UV/visible spectrophotometer was used to read the absorbance of the filtrate and via calibration plot of the standard, the concentrations were determined.

Amlodipine besylate tablets' dissolution studies

USP <711> apparatus type II, at 75 rpm (Erweka DT700, Husenstamm, Germany) with six replicates was used to determine in vitro release of Amlodipine besylate tablets (5 mg). 900 mL distilled water, maintained at 37 ± 0.5 °C, was used as dissolution medium. For 2 h (i.e. 5, 10, 15, 20, 25, 30, 45, 60 and 120 minutes), 10 ml aliquots were withdrawn and replaced with fresh distilled water. The samples were then filtered. Same procedure as mentioned above was followed for 0.1 N hydrochloric acid (pH 1.2), acetate buffer of pH 4.5 and phosphate buffer of pH 6.8 USP. UV Spectrophotometer (150-02, Shimadzu Corporation, Kyoto, Japan) at 239 nm was used for the samples and cumulative percentages of the drug dissolved from the tablets were calculated.

Data analysis for Amlodipine besylate (5 mg) tablets

A model independent approach is recommended by US FDA guidance for dissolution data equivalence involving use of similarity factor (f2) [21]. The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the dissolution (%) of two curves (Eq. 1).

$$f_2 = 50 \times \log \left\{ \left(1 + \frac{1}{N} \sum_{t=1}^{n} \left(R_t - T_t \right)^2 \right)^{-0.5} \times 100 \right\}$$

where N is the number of dissolution sample times and Rt and Tt are the individual or mean percents dissolved at each time point for the reference and test products respectively.

The difference factor can also be calculated using (Eq. 2) as follows

$$f_1 = \left\{ \left(\sum_{t=1}^{n} |R_t - T_t| \right) \Big/ \sum_{t=1}^{n} R_t \right\} \times 100$$

where Rt and Tt are the percentage release of reference and test brands respectively.

The main advantage of both equations is that they provide a simple way to compare the data. According to the FDA guidance, f2 values from 50-100 % ensure similarity and f1 values less than 50 % ensure the dissimilarity of two dissolution profiles. The dissolution profiles may be established as comparable without additional mathematical estimation when drug dissolution is more than 85% within 15 minutes [22].

RESULTS AND DISCUSSION

This study was conducted to assess the quality of different brands of Amlodipine Besylate (5mg) tablets and also to determine the suitability for inter-changeability. Six brands of Amlodipine Besylate (5 mg) tablets with their label information and cost comparison are in Table 1. In Pakistan, majority of the population is not able to bear the cost of expensive medication. It can be seen from Table 1 that the innovator brand is 45% more expensive than the test brands. The lowest price brand was brand C (Rs. 11.5 per 10 units) whose results showed more or less the same release kinetics and hence can be used inter-changeably with the expensive brands.

Results of Quality control studies

It is important to perform physical testing of the dosage forms for the establishment of a meaningful correlation between physical characteristics and in vitro release of the drug. This facilitates in understanding drug's in vivo bioavailability. The physicochemical parameters were given much importance in many studies for establishing a safe and effective drug product [23-28]. All Amlodipine besylate brands were evaluated for physical testing. The weight variation of brands from A to F showed mean weights of 209.20±7.32, 186.60±4.28, 161.50±5.31, 137.45±3.08, 182.15±5.25 and 202.85±4.60 respectively which were within the limit of ± 10 % USP as shown in Table 2. Hardness and friability results were from 1.53-8.77 kg/cm2 and less than 1% respectively. Tablets diameters, length and breadth were found within the specified limits as shown

in Table 2. No significant difference was found in between the different brands.

The results obtained from quality control test i.e. disintegration test and content uniformity were less than 15 min and 98.96-100.76 %, respectively as shown in Table 2. The physicochemical characteristics of the five generic brands tested were all within the BP limits for immediate release dosage forms; these declare pharmaceutical equivalence of Amlodipine besylate generics tested with the innovator.

Table 1: Label Information of Six Brands of Amlodipine Besylate Tablets (5mg)

S. No.	Brand Code	Lot no/ Batch no	Manufacturing date	Expiry date	Price/10 units (PKR)	Price differential with innovator (%)
1	Brand A	033T46	November 2010	November 2012	119	Innovator
2	Brand B	MT – 627	November 2010	November 2012	50	57.98
3	Brand C	140	November 2010	November 2013	11.5	90.33
4	Brand D	3615	January 2011	January 2013	52.5	55.88
5	Brand E	10005	November 2010	November 2013	65.21	45.20
6	Brand F	1005043	December 2010	December 2013	59.5	50.00

Table 2: Physiochemical Characteristics of Selected Brands of Amlodipine Besylate (5mg) Tablets

S. No.	Brand Code	Average Weight ± S.D (mg)	Average Thickness ± S.D (mm)	Average length ± S.D (mm)	Average breadth± S.D (mm)	*Hardness±S.D kg	Friability	Mean Disintegration Time ± S.D (Sec)	Assay ± S.D (%)
1	Brand A	209.20±7.32	3.72±0.05	9.07±0.04	6.88±0.04	2.80±0.10	0.58	16±0.30	98.96±0.91
2	Brand B	186.60±4.28	3.09±0.08	8.34±0.05	6.74±0.19	8.77±0.64	0.26	26±0.27	99.01±0.76
3	Brand C	161.50±5.31	3.76±0.05	9.85±0.18	6.83±0.04	7.57±0.05	0.62	30±0.19	99.47±0.64
4	Brand D	137.45±3.08	2.96±0.06	9.34±0.07	4.39±0.02	5.92±0.07	0.36	24±0.41	100.76±0.55
5	Brand E	182.15±5.25	4.47±0.09	----	-----	1.53±0.36	0.91	19±0.88	99.00±0.02
6	Brand F	202.85±4.60	3.23±0.07	8.78±0.10	-----	2.80±0.10	0.49	32±0.81	99.3±0.61

(Result based on n=20 and * n=10)

Table 3: Dissolution Amount ("Rapidly Dissolving", "Very Rapidly Dissolving" Or "Not Very Rapidly Dissolving") For Evaluated Amlodipine besylate (5 mg) tablets.

Medium	Brand Code	% Dissolved (X̄) 15 Min	% Dissolved (X̄) 30 Min
Distill Water	Brand A	91.89	96.04
	Brand B	97.73	98.36
	Brand C	87.61	94.81
	Brand D	88.47	96.23
	Brand E	87.53	93.91
	Brand F	88.69	93.33
pH 1.2	Brand A	91.96	92.76
	Brand B	97.6	98.42
	Brand C	85.1	89.56
	Brand D	86.28	92.16
	Brand E	90.72	96.81
	Brand F	90.49	96.83
pH 4.5	Brand A	95.32	96.08
	Brand B	87.00	92.06
	Brand C	85.07	90.13
	Brand D	85.63	87.42
	Brand E	88.57	96.13
	Brand F	91.33	94.61
pH 6.8	Brand A	87.28	90.6
	Brand B	85.06	87.83
	Brand C	86.82	92.16
	Brand D	85	86.2
	Brand E	86.08	92.17
	Brand F	85.91	92.27

Dissolution studies of Amlodipine besylate (5 mg) brands

Biowaiver criteria for drugs containing BCS Class I active pharmaceutical ingredients (1) are defined by WHO (World Health organization):

1. The dosage form is rapidly dissolving (dissolution amount is greater than 85% at 30 min in all media with pH 1.2, 4.5, 6.8) and the dissolution profile of the test product is comparable to that of the reference product using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile resemblance, f2 ≥ 50 (or equivalent statistical criterion);

2. If both the test and the reference dosage forms are very rapidly dissolving having dissolution quantity greater than 85% at 15 min in all media with pH 1.2, 4.5, 6.8, then a profile comparison is not essential. Different brands of Amlodipine Besylate tested were "very rapidly dissolving" as seen from Table 3, because more than 85% of the active pharmaceutical ingredient released at time point 15 minutes.

They are considered to be in vitro equivalent without in vivo evaluation, hence therapeutically equivalent. Amlodipine Besylate is "highly soluble" and "highly permeable" [29, 30]. Dissolution profiles and corresponding data of Amlodipine besylate (5 mg) tablets can be seen from Table 4. Dissolution profiles of all the test and generic brands were comparable and showed that more than 85% drug released in 15 min in distilled water, pH 1.2, 4.5 and pH 6.8 buffers.

The percent relative standard deviation (% RSD) for all time points (≤20% for 15 min, ≤10% for other time points) showed valid results (Table 4)

Table 4: Dissolution Test Results for Amlodipine besylate (5 mg) Tablets

Medium	TIME (Min)	Brand A		Brand B		Brand C		Brand D		Brand E		Brand F	
		% Dissolved (X̄)	RSD (%)	% Dissolved (X̄)	RSD (%)	% Dissolved (X̄)	RSD (%)	% Dissolved (X̄)	RSD (%)	% Dissolved (X̄)	RSD (%)	% Dissolved (X̄)	RSD (%)
Distill Water	5	88.7	2.87	96.05	4.61	87.61	2.30	80.89	2.52	83.47	2.26	87.24	2.68
	10	92.07	3.18	97.25	2.41	90.47	2.81	82.77	4.01	86.95	3.94	87.75	4.25
	15	91.89	2.76	97.73	2.00	87.61	1.82	88.47	4.12	87.53	2.07	88.69	4.87
	20	92.35	3.32	97.86	3.91	90.79	3.84	92.77	3.66	90.14	1.67	89.27	2.54
	25	95.36	2.00	98.15	2.78	93.65	2.02	93.99	2.64	91.01	1.35	92.46	2.00
	30	96.04	3.30	98.36	1.42	94.81	4.71	96.23	1.36	93.91	3.26	93.33	2.61
	45	96.63	3.05	99.44	2.49	96.85	1.39	96.1	3.81	93.99	2.22	97.1	3.38
	60	98.51	3.28	98.88	1.89	98.07	6.57	98.04	5.67	97.36	1.88	100.01	2.87
	120	98.08	3.23	99.92	3.88	98.54	5.73	99.44	2.17	98.55	2.25	100.87	2.28
pH 1.2	5	89.23	3.85	94.23	4.64	80.8	2.80	79.81	2.19	88.11	2.00	86.71	1.71
	10	91.15	6.00	96.49	3.99	82.74	2.85	81.84	2.22	89.97	4.44	88.93	3.93
	15	91.96	3.67	97.6	3.89	85.1	3.61	86.28	3.62	90.72	2.70	90.49	3.49
	20	92.44	1.60	97.7	4.00	85.71	1.35	86.57	4.48	94.78	5.76	92.84	3.51
	25	92.52	1.68	98.57	4.64	86.21	1.66	86.9	2.66	96.52	6.52	94.12	2.70
	30	92.76	3.91	98.42	6.00	89.56	2.10	92.16	2.17	96.81	2.45	96.83	1.67
	45	93.66	2.18	99.2	3.85	92.99	2.04	96.51	3.76	97.97	2.25	98.49	3.74
	60	96.41	3.35	99.85	3.18	96.16	3.10	99.01	2.78	99.71	3.93	98.22	2.59
	120	99.02	4.34	100.19	3.24	96.51	2.94	99	1.01	100.58	2.72	100.75	4.20
pH 4.5	5	92.11	2.77	82.67	3.91	78.59	4.37	81.12	6.59	85.41	1.04	86.98	3.42
	10	95.01	2.41	84.23	2.87	84.5	4.09	81.4	5.36	87.81	2.51	88.6	2.55
	15	95.32	2.28	87	2.15	85.07	2.31	85.63	2.08	88.57	3.87	91.33	2.08
	20	96	2.48	90.04	3.14	86.47	4.12	85.99	2.07	90.45	3.52	92.92	3.69
	25	96.18	2.23	92.77	5.91	87.04	2.48	87.32	3.47	92.78	3.81	92.96	4.58
	30	96.08	1.49	92.06	3.73	90.13	3.53	87.42	4.62	96.13	4.17	94.61	5.39
	45	96.71	3.36	95.82	2.72	94.08	1.29	94.66	3.50	98.36	2.21	95.05	2.01
	60	99.59	3.74	96.41	1.33	94.36	5.60	96.2	3.14	99.51	2.82	98.8	1.47
	120	99.3	3.36	97.01	1.91	96.62	3.36	98	3.04	100.14	2.31	99.98	1.68
pH 6.8	5	80.3	4.71	79.15	2.95	78.3	2.71	74.6	2.92	78.55	1.02	76.24	2.55
	10	83.35	2.91	82.63	4.62	79.81	2.55	79.48	1.66	83.47	2.40	83.87	3.51
	15	87.28	2.64	85.06	3.41	86.82	3.74	85	4.85	86.08	3.22	85.91	2.87
	20	87.34	3.38	85.73	3.05	85.39	1.51	85.71	3.70	88.69	5.12	87.79	2.96
	25	89.23	2.51	86.17	1.09	86.57	3.02	86.51	2.42	91.1	2.26	88.69	2.80
	30	90.6	2.10	87.83	2.66	92.16	2.17	86.2	2.79	92.17	2.70	92.27	3.91
	45	92.91	3.14	89.15	6.92	94.26	2.99	89.55	3.20	94.7	3.74	94.24	3.14
	60	94.67	4.24	90.81	4.77	96.51	4.20	95.29	2.07	94.44	1.17	94.1	4.78
	120	96.87	3.86	91.51	3.99	96.91	5.01	97.53	2.00	96.81	3.19	95.32	2.81

CONCLUSION

Price differential between generic brands does not necessarily mean low quality for the cheaper brand. So as to have appropriate generic product selection, all health care professionals require ample information on inter-changeability for substitution of products. It is important that such facts and figures regarding generic substitution of products be available by the regulatory agencies so that product selection is objective.

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