dx.doi.org/10.14227/DT280421PGC1

Quality Attributes and In Vitro Bioequivalence of Amlodipine (5 mg) Tablets in Ica, Peru

Jorge A. García[1], María R. Bendezú[1], Mario Pineda-Pérez[2], Ana María Muñoz[3], María Saravia[4], and Angel T. Alvarado[4*]

[1]*Faculty of Pharmacy and Biochemistry, San Luis Gonzaga National University of Ica, Ica, Peru.*
[2]*Peruvian Association of Immunogenomics and Personalized Medicine, Lima, Peru.*
[3]*Research Unit in Nutrition, Health Functional Foods and Nutraceuticals, San Ignacio de Loyola University, Lima, Peru.*
[4]*International Network for Research in Pharmacology and Precision Medicine (REDIFMEP), San Ignacio de Loyola University, Lima, Peru.*

e-mail: eaa.alvarado@hotmail.com

ABSTRACT

Dissolution studies have evolved from quality control testing to being an indicator of biopharmaceutical performance and an alternative to in vivo bioequivalence and interchangeability studies in clinical practice. The critical quality attributes and in vitro bioequivalence of two generic formulations of amlodipine (5-mg tablets, A and B) were compared to the reference (Ref) drug. Amlodipine tablets available in Ica, Peru belong to class 1. The study evaluated weight, hardness, friability, and content of the tablets. USP apparatus 2 was used with 900 mL of dissolution medium at pH 1.2, 4.5, and 6.8. 5 (100 rpm, 37 ± 0.5 °C). Samples (5 mL) were withdrawn at 5, 10, 15, 20, 25, 30, 45, and 60 min and analyzed at 239 nm on a spectrophotometer. The dissolution percentages at pH 4.5 and 6.8 were less than 85% at 30 min for all three products; at pH 1.2, more than 85% was released in less than 15 min (Ref: 101.6%; A: 98.5%, B: 89.9%). The similarity factors were 51.2–64.3; dissolution efficiency was 84.5–96.5%, and mean dissolution time was 4.5–12.4 min. According to these parameters, generic formulations A and B demonstrated in vitro bioequivalence to the reference drug.

KEYWORDS: Amlodipine, quality control, dissolution, bioequivalent drug, drug interchangeability

INTRODUCTION

The bioequivalence or therapeutic equivalence of generic drugs can be performed through in vivo and in vitro studies. In vivo bioequivalence can be through relative bioavailability (pharmacokinetics), pharmacodynamics, or clinical studies, the same as that applied for class 2 (low solubility and high permeability) and class 4 (low solubility and low permeability) of the Biopharmaceutical Classification System (BCS) (*1–5*). In these studies, the metabolic phenotype of the volunteer should be considered, that is, if it is an extensive, slow, or fast metabolizer, because it influences the bioavailability of the drug, affecting therapeutic equivalence and interchangeability in clinical practice (*6*). Although in vitro bioequivalence studies are performed for class 1 (high solubility and high membrane permeability) and class 3 (high solubility and low membrane permeability) drugs, according to BCS, the same is carried out in three dissolution media at pH 1.2, pH 4.5, and pH 6.8, comparing the dissolution profiles of

*Corresponding author

the generic with the reference (*3*, *5*). Amlodipine (3-ethyl-5-methyl-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate) is a class 1 dihydropyridine according to BCS, a calcium channel blocker, and due to its lateral amino group, it presents a pKa of 9.4; therefore, it is absorbed from the intestinal mucosa, obtaining bioavailability of 60–65%, indicating good solubility and permeability and low intestinal metabolism due to the action of cytochrome P450 3A4 (CYP3A4) despite the fact that said enzyme is expressed in intestinal epithelial cells (*7*–*11*). The maximum plasma concentration (C_{max}) is 5.87 ng/mL, reached in a maximum time (t_{max}) of 5–8 hours (*9, 12*). The steady state is generated between 6 and 12 hours, it circulates 98% bound to plasma proteins, and its volume of distribution (Vd) is 21 L/kg (*10*, *13*). It is metabolized at the hepatic level by phase I with the participation of CYP3A4 that oxidizes the amino group of the 2-aminoethoxymethyl side chain and the 3-methylcarboxylate, originating from an inactive metabolite (*8, 11*). Its elimination half-life ($t_{1/2}$) is 34–50 hours, so it is administered in a single dose per day, and in case of liver failure, the plasma concentrations rise and the half-life is prolonged up to 60 hours; its metabolites are eliminated in the urine, and 10% of the drug is unchanged (*9*, *10*, *12*, *13*).

For in vitro bioequivalence studies for class 1, the BCS guidelines must be met, which indicate that the test drug as the reference must be rapidly dissolving (drug release ≥ 85% of active pharmaceutical ingredient (API) in ≤ 15 min) or fast dissolving (≥ 85% release of the API in ≤ 30 min) (*5*). Additionally, the biopharmaceutical phase of the tablets (disintegration, disaggregation, and dissolution) can be evaluated, which is determined by the hardness and other technological production processes (*14*, *15*, *16*).

In developing countries like Peru, commercialization of drugs of doubtful origin and counterfeit drugs, i.e., without API or with insufficient amounts of API, has been evidenced, which is a global public health problem (*17*, *18*). With the Ministry of Health's list of generic essential drugs in international common denomination, prescribing and dispensing of generic drugs in private and public pharmacies is promoted; and for the acquisition of drugs, pharmaceutical laboratories carry out and comply with quality control tests described in the official pharmacopoeias, but in vitro and in vivo bioequivalence studies are required (*19*).

Until now, publications of in vitro and in vivo bioequivalence studies are scarce in Peru, which is why it is necessary to carry out these studies, mainly for the drugs that are in the Ministry of Health's list of essential drugs. Results of these studies form the scientific evidence needed to encourage the implementation of relative bioavailability studies, mainly in vitro bioequivalence studies, in Latin America as a practical and economical alternative to guarantee interchangeable generic drugs products in clinical practice (*15*, *16*). Therefore, the objective of the present study was to evaluate the critical quality attributes and in vitro bioequivalence of two generic formulations of amlodipine (5-mg tablets) and a reference drug, comparing statistical indicators of equivalence such as the similarity factor (f_2), dissolution efficiency (DE), and mean dissolution time (MDT).

MATERIALS AND METHODS

Chemicals and Reagents

All substances and reagents were of analytical grade and ACS (American Chemical Society) quality, acquired from Mercantil Laboratory SAC (Lima, Peru), preserved at analytical laboratory conditions (temperature 20 °C and humidity 40%): hydrochloric acid (HCl) 36%, anhydrous sodium acetate (CH_3-COONa), sodium hydroxide (NaOH), monobasic potassium phosphate (KH_2PO_4), and amlodipine besylate standard USP (United States Pharmacopeia). Chromafil syringe filters (0.45-µm pore/25 mm) were used.

Collection of Samples

The study samples (200 5-mg amlodipine besilate tablets; two generic and reference products) were purchased from a pharmacy in Ica, Peru. The tablets were randomly labeled generic "A" (Nat, Lot 2026400, RS EN-00369, expiration date 02/2023) and "B" (Pharm, Lot 10898039, RS EN-05266, expiration date 08/2021), and the reference drug was coded as "R" (Norvasc, Pfizer, Lot 00021003, RS E-16165, expiration date 03/2023). All trials were conducted within the shelf life of the drugs.

Method Validation and Calibration

The dissolution method was validated using 50-mg propylthiuracil tablets by spectrophotometry (Unico Model UV 2100 Series, USA) at a wavelength of 239 nm, evaluating specificity (to find interference from excipients and the API in the tablets), and linearity (range, 1.60–7.75 µg/mL). Interday precision was evaluated with six tablets (*15*, *20*).

Calibration of the dissolution apparatus (Electrolab ETC-11Lx, Model 1104197, Series 1201044, India) was performed with USP 10-mg Prednisone RS tablets (Lot R080J1), 500 mL of purified water at 37 ± 0.5 °C for 30 minutes The distance between the lower part of the paddle and bottom of dissolution vessel was 25 ± 2 mm. The qualification of the isothermal medium was carried out by setting the temperature selector at 37 °C, which verifies uniformity of the heated water bath (thermal convection heats distilled water that surrounds the dissolution glass and purified water inside the glass) (*15, 20*).

Weight Variation Determination

Twenty tablets were randomly selected from each study sample (generic and reference) and weighed individually on an analytical balance (Boeco BBL31, Germany), the acceptance criterion being standard deviation < 5% (*15, 20–22*).

Hardness Test

Twenty tablets were randomly selected from each brand of amlodipine to determine the hardness in a hardness tester (BIOBASE THAT-3, China), with an acceptance limit of 6 ± 2 kgf (*15, 20–22*).

Friability Test

After randomly selecting 20 tablets of each brand of amlodipine, tablets were weighed (*W1*) and immediately placed in a friability tester (Erweka TAR, Germany) programmed at 25 rpm for 4 min, after which the tablets were dusted and weighed (*W2*). The

percentage of acceptance due to friction loss (F) was calculated by applying the following equation: F = [(*W1* – *W2*) / (*W1* × *W2*)] × 100. The acceptance criterion was < 1% (*15, 20–22*).

Content

The average weight of 20 tablets of amlodipine (5 mg each) was determined. The tablets were then crushed to make a fine powder, and 0.15 g equivalent weight of amlodipine powder was transferred to a 200-mL volumetric flask. To make solution A, 50 mL of 0.1 N NaOH was added and mixed, followed by addition of 100 mL of distilled water. The suspension was immediately subjected to the action of ultrasound (Ultrasound, Lab Companion, UC-10, JT-11AB-078-YP series, Korea) for 15 minutes then allowed to cool to room temperature and made up to 200 mL with distilled water. To make solution B, 10 mL of solution A was measured, filtered, and made up to 100 mL with distilled water; 10 mL of solution B plus 10 mL of 0.1 N NaOH were taken and transferred to a 100-mL volumetric flask, mixed, and gauged with distilled water, obtaining a final concentration of 0.0075 mg/mL. The final solution was filtered to read the absorbance in triplicate at a wavelength of 239 nm using distilled water as a blank (*21, 22*).

Dissolution Tests

To obtain the dissolution profile, 12 tablets were used for each formulation of amlodipine (A B, and Ref). USP apparatus 2 (paddle) was used with 900 mL of dissolution medium (HCl pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8) at 37 ± 0.5 °C and 100 rpm (to avoid the formation of cones, which can occur at the speed of 50 rpm and affect the dissolution results) for 60 min. Deaeration of the dissolution media was performed under vacuum, passing the liquid through a 0.45-µm membrane filter while sonicating with a water bath in ultrasound (Ultrasound, Lab Companion, UC-10, JT-11AB-078-YP series, Korea) (*21, 22*).

Samples (5-mL) were extracted through 0.45-µm chromafil filters at preset timepoints, 5, 10, 15, 20, 25, 30, 45, and 60 min, without medium replacement. The absorbance´s were determined by UV/Vis spectrophotometry at a wavelength of 239 nm, and freshly prepared medium was used as a blank. A calibration curve with an R^2 value of 0.99 was applied to calculate the concentration and percentage of content.

Statistical Analysis

SPSS 23 and Microsoft Office Excel 2007 were used for statistical analysis. As a statistical indicator of in vitro biopharmaceutical equivalence, f_2, DE, and MDT were analyzed (*2, 15, 16, 20*).

DE was determined with the formula: $(AUC_o^t \times 100) / Q^\infty \times t^\infty$, where AUC_o^t is the area under the release curve from the initial time to the final time of the experiment; Q^∞ is the mean amount of the drug obtained at the end time of the experiment; and t^∞ is the end time of the experiment.

MDT was estimated with the formula: $\Sigma_i t_i \Delta Q\ (t_i) / Q^\infty$, where $\Sigma_i t_i \Delta Q\ (t_i)$ is the sum of the difference in time and mean amount of drug, and Q^∞ is the mean amount of the drug obtained at the end of the experiment (*2, 15, 16, 20*). Analysis of variance (ANOVA) was performed including the drug and pH as independent variables (*15, 20*).

Dunnett's test was used to compare the innovator with the other formulations. A *p*-value < 0.05 was considered significant (*2, 15*).

RESULTS

Results of the hardness, weight, friability, and content tests are presented in Table 1. Average hardness values were within the acceptance criterion (6 ± 2 kgf; CV% < 4%). Weight variation was acceptable. All results had an SD of less than 5%, indicating reproducibility within and between batches. Friability test results were within acceptable limits (< 1% loss due to friction). All formulations met the requirements for drug content (i.e., 90–110% of the label amount).

Table 1. Quality Control Characteristics of 5-mg Amlodipine Immediate-Release Tablets (n = 20)

Product	Hardness (< 6 kg-f)		Weight (CV < 4%)		Friability (< 1%)	Content (%)
	Mean± SD (kgf)	CV%	Mean ± SD (mg)	CV%		
Generic A	5.36 ± 0.06	1.08	24.99 ± 0.36	1.46	0.15	110.0
Generic B	5.72 ± 0.07	1.16	99.96 ± 0.60	0.60	0.28	101.0
Reference	4.69 ± 0.13	2.84	50.01 ± 0.43	0.86	0.13	101.0

CV%: coefficient of variation

Table 2 shows the percentages of drug release for the 5-mg amlodipine besylate tablets in three pH levels. At pH 1.2, all three products showed more than 85% release in less than 15 min (CV < 4%). At pH 4.5 and pH 6.8, drug release was less than 85% at all timepoints for all three products.

Table 2. Dissolution Test Results for 5-mg Amlodipine Immediate-Release Tablets at pH 1.2, 4.5, and 6.8

Time (min)	Reference Product		Generic A		Generic B	
	Mean (%)	CV%	Mean (%)	CV%	Mean (%)	CV%
Dissolution medium: Hydrochloric acid, pH 1.2						
5	99.6	1.38	98.7	0.43	84.7	0.89
10	101.1	1.12	97.8	1.52	84.6	1.08
15	101.6	0.52	98.5	1.81	89.9	2.75
20	101.8	0.48	100.2	0.06	91.6	2.89
25	101.7	0.93	100.2	0.06	92.3	3.66
30	102.3	1.22	101.9	1.03	94.1	3.25
45	100.4	2.56	102.6	0.39	94.7	3.01
60	100.4	2.56	101.9	0.63	96.1	2.23
Dissolution medium: Acetate buffer, pH 4.5						
5	72.9	2.81	65.5	3.03	61.3	3.78
10	73.6	3.42	68.3	2.44	66.7	3.20
15	74.8	3.75	68.6	3.34	67.6	3.64
20	76.3	3.87	70.7	3.10	68.3	2.94
25	77.4	3.96	70.8	3.39	69.6	2.25
30	81.2	3.68	71.4	1.51	74.5	3.48
45	83.6	3.88	72.7	1.55	75.6	3.47
60	84.7	3.97	73.6	2.13	76.0	4.81
Dissolution medium: Phosphate buffer, pH 6.8						
5	70.3	2.07	65.1	1.74	57.4	3.88
10	71.8	2.98	70.4	3.17	60.6	2.19

15	73.1	3.57	73.1	2.90	63.3	2.90
20	74.3	3.10	74.4	2.45	66.5	3.75
25	75.6	2.97	75.9	2.46	69.1	2.69
30	79.3	3.33	79.1	1.12	74.3	3.45
45	88.3	3.09	79.9	0.60	78.3	3.17
60	91.2	2.04	80.5	1.22	80.8	2.51

Figure 1 shows the dissolution profiles of generic formulations A and B of amlodipine (5 mg) compared to the reference. Each point of the profile represents the mean of the percentage of dissolution of the tablets, at each sampling time, and the corresponding error bars (SD).

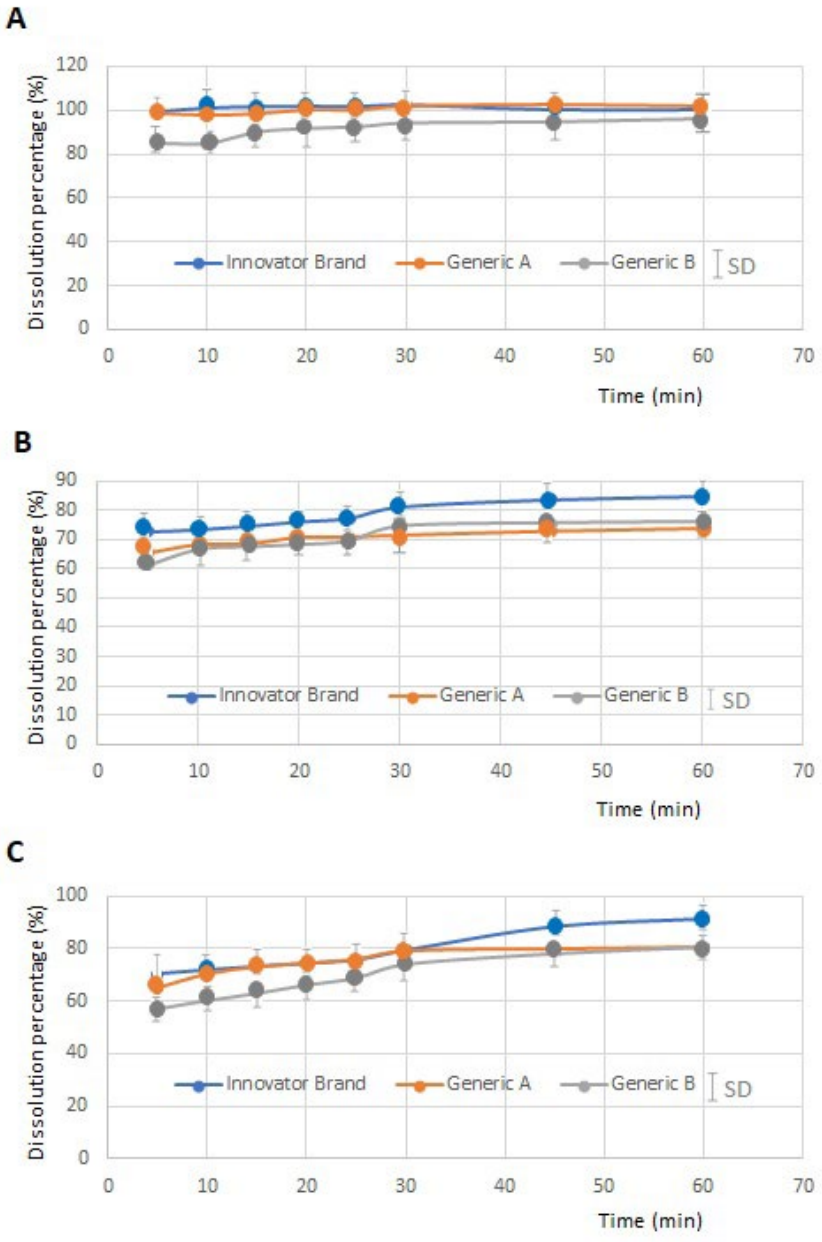

*Figure 1. Dissolution profile (mean ± SD) of 5-mg amlodipine tablets at pH 1.2 (**A**), 4.5 (**B**), and 6.8 (**C**).*

The parameters that characterize the drug release curve for 5-mg amlodipine formulations in three dissolution media were determined, i.e., f_2, DE, and MDT. The f_2 values were within the acceptance range of 50-100 (Table 3). DE values ranged from 84.5-96.5%, with the highest values at pH 1.2 (Ref: 96.5%; A: 94.8%, B: 91.9%) and lowest at pH 6.8 (Ref: 84.5%; A: 90.8%, B: 84.7%), and MDT values ranged from 4.5 to 12.4 min.

Table 3. Similarity Factor (f_2), DE, and MDT Values for 5-mg Amlodipine Immediate-Release Tablet Formulations

Product	f_2 (%)		AUC_o^t (min%)			DE (%)			MDT (min)		
pH	4.5	6.8	1.2	4.5	6.8	1.2	4.5	6.8	1.2	4.5	6.8
Generic A	54.3	64.3	5798.2	4074.3	4388.3	94.8	92.3	90.8	5.6	7.3	8.1
Generic B	54.2	51.2	5295.7	4115.4	4107.1	91.9	90.2	84.7	7.5	8.5	12.1
Reference			5810.7	4575.9	4627.6	96.5	90.0	84.5	4.5	8.7	12.4

AUC_o^t: area under the curve by the trapezius method, DE: dissolution efficiency, MDT, dissolution efficiency.

DISCUSSION

In the present investigation, amlodipine besylate, which belongs to class I of the BCS, was evaluated to determine if the formulations of national production have efficient dissolution and if their absorption limits bioavailability; we have previously carried out quality control tests, reporting low variability in the weights of the study samples, ensuring reproducibility within and between batches (*23*). Hardness values were below 6 kgf ± 2 kgf in all the formulations studied, demonstrating homogeneity within the production batch (*15, 20*). Friability values indicate that the surfaces of the tablets are not fragile to handling, because no cracked or broken tablets were evident after the test (< 1% wear). Content of the tablets was within acceptable values (90–110%) according to USP, indicating efficacy and stability of the product (*2, 21, 22*). These results demonstrate that both generic amlodipine (5 mg) formulations tested meet the critical quality attributes.

The dissolution profile was evaluated at eight sampling points, following the criteria proposed for class 1 according to BCS performed at three pHs, which simulate the physiological conditions of the gastrointestinal tract, allowing for prediction of optimal absorption of the drug in vivo (*24*). The dissolution percentages found for the drugs investigated at pH 4.5 and 6.8 were less than 85% at 15 min; however, the coefficients of variation (CV%) were less than 4.81% up to 60 min, complying with the acceptance criteria for class 1 drugs, in which it is indicated that the CV% should not be higher than 20% from baseline to 10 min, and should not be more than 10% at other time points (*5*).

By applying the Henderson-Hasselbach equation (pH = pKa + log [*I* / *NI*]) for the dissolution medium of pH 1.2 and for amlodipine of pKa 9.4, a higher percentage of the ionized form of the drug (I) was obtained. This is directly proportional to solubility, so we observed a high percentage of dissolution of the generic and reference products at pH 1.2 (15 min: Ref: 101.6%; A: 98.5%, B: 89.9%). These findings are supported by the USP, which recommends performing the dissolution tests of amlodipine tablets in an acidic dissolution medium (pH 2; 0.01 N) so that it releases the API in a percentage not

less than 75% in 30 min. Drug release differs with respect to the volume (500 mL) and rotation speed (75 rpm), and in the present study a volume of 900 mL and a speed of 100 rpm were used (*21, 22*). Additionally, Dressman et al. reported that the change in pH affects the solubility of drugs and therefore their oral bioavailability; Markopoulos et al. reported that pH is a determining factor of dissolution profiles; and Krieg et al. demonstrated that the dissolution medium influences the biopharmaceutical phase of drugs (*24–26*).

To demonstrate bioequivalence in vitro, f_2, DE, and MDT were studied for the three amlodipine tablets. The dissolution profiles of generic A and B are similar to the reference at pH 4.5 and 6.8 because f_2 is within the range of 50–100. The percentage difference was less than 10% for A (pH 4.5, f_2: 54.3; pH 6.8, f_2: 64.3) and B (pH 4.5, f_2: 54.2; pH 6.8, f_2: 51.2). If the similarity factor is 65, the difference is 5%, and when f_2 is 50, the difference is 10% (*2, 5, 15, 20*). It was not necessary to determine f_2 at pH 1.2, because all the formulations of the study released more than 85% in less than 15 min. However, care must be taken against an incorrect decision of bioequivalence when the generic formulation is suprabioavailable because it can release a high amount of API that in vivo would indicate a high concentration of drug in the biophase and would generate toxicity (*16*). DE values in the three dissolution media were greater than 84.5%. This parameter directly correlates with the degree of absorption of a drug, because dissolving more than 63.2% of a tablet ensures that a dissolved amount of drug will be in contact with the intestinal mucosa for absorption (*20, 27*). MDT values were below 12.4 min. MDT correlates with mean gastric emptying (residence time), which under fasting conditions is 15–20 min. Therefore, we can confirm that dissolution of generics A and B and the reference would release the API in the appropriate times (*2, 15, 20*). Taken together, f_2, DE, and MDT values indicate the in vitro bioequivalence of the generic formulations with the reference, which has an implication in clinical practice because they are interchangeable, having bioavailability of 65% and obtaining a plasma level within the therapeutic margin, thus guaranteeing pharmacological efficacy and minimizing adverse effects.

The limitations of our study are in the sample size (only two generic brands), not having evaluated all the generic and commercial brand drugs available in the Peruvian pharmaceutical market, and not having performed the disintegration test, which should be considered in future studies. Notwithstanding the foregoing, we consider that this study is relevant because it contributes to in vitro bioequivalence studies that are scarce in the country, providing scientific evidence to support regulatory authority requirements for in vivo and in vitro bioequivalence studies before obtaining the sanitary registration and before bidding for the acquisition of medicines, to guarantee the availability and access of interchangeable medicines for people with fewer economic resources in Peru.

CONCLUSION

In conclusion, the current study indicates that the generic formulations A and B of 5 mg amlodipine besylate demonstrate in vitro bioequivalence with respect to the reference, determined by f_2, DE, and MDT. However, it should be noted that at pH 4.5 and 6.8, none of the three products tested showed drug release greater than 85% in less than 30 min. Considering this case study, the regulatory authorities of Peru should exercise

caution, and in vitro bioequivalence studies are highly recommended as an additional quality control tool to detect quality failures during formulation research activities in developmental stages as well as commercial manufacturing.

FUNDING

This work was supported by the Peruvian Association of Immunogenomics and Personalized Medicine and San Ignacio de Loyola University School of Human Medicine.

CONFLICTS OF INTEREST

The authors disclosed no conflicts of interest related to this article.

REFERENCES

1. *Bioavailability And Bioequivalence Studies for Orally Administered Drug Products-General Considerations*; Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, July 2002.
2. Alvarado, A. T.; Muñoz, A. M.; Miyasato, J. M.; Alvarado, E. A.; Loja, B.; Villanueva, L.; Pineda, M.; Bendezú, M.; Palomino-Jhong, J. J.; García, J. A. In vitro therapeutic equivalence of two multisource (generic) formulations of sodium phenytoin (100 mg) available in Peru. *Dissolut. Technol.* **2020**, *27*, 33–40. DOI: 10.14227/DT270420P33.
3. Shah, V. P.; Amidon, G. L. G.L. Amidon, H. Lennernas, V.P. Shah, and J.R. Crison. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, *Pharm Res* 12, 413-420, 1995--backstory of BCS. *AAPS J.* **2014**, *16*, 894–898. DOI: 10.1208/s12248-014-9620-9.
4. WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*; WHO Technical Report Series, No. 1003, Annex 6; World Health Organization: Geneva, 2017.
5. *ICH M9 Guideline on Biopharmaceutics Classification System-Based Biowaivers*; EMA/CHMP/ICH/493213/2018; Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency: London, 2020.
6. Alvarado, A. T.; Muñoz, A. M.; Loja, B.; Miyasato, J. M.; García, J. A.; Cerro, R. A.; Quiñones, L. A.; Varela, N. M. Study of the allelic variants CYP2C9*2 and CYP2C9*3 in samples of the Peruvian mestizo population [in Spanish]. *Biomédica* **2019**, *39*, 601–610. DOI: 10.7705/biomedica.4636.
7. *Resolution No. 53/2007. Regulation 48/2007. Requirements to apply and/or Design a Dissolution Test in Capsules and Immediate Release Tablets. Resolution No. 82/200* [in Spanish]*;* Regulatory Scope Bulletin, Centro Para el Control Estatal de la Calidad de los Medicamentos, Oct 18, 2007.
8. Park, J. W.; Kim, K. A.; Il Kim. Y.; Park, J. Y. Pharmacokinetic and haemodynamic interactions between amlodipine and losartan in human beings. *Basic Clin. Pharmacol. Toxicol*. **2019**, *125*, 345–352. DOI: 10.1111/bcpt.13244.
9. Kim, S.; Ko, J. W.; Kim, J. R. Pharmacokinetic and safety profiles of a fixed-dose combination of amlodipine, valsartan, and atorvastatin: a 3-period replicate crossover study. *Clin. Pharmacol. Drug Dev.* **2020**, *9*, 386–394. DOI: 10.1002/cpdd.727.
10. Meredith, P. A.; Elliott, H. L. Clinical pharmacokinetics of amlodipine. *Clin. Pharmacokinet.* **1992**, *22*, 22–31. DOI: 10.2165/00003088-199222010-00003.
11. Saiz-Rodríguez, M.; Almenara, S.; Navares-Gómez, M.; Ochoa, D.; Román, M.; Zubiaur, P.; Koller, D.; Santos, M.; Mejía, G.; Borobia, A.M.; Rodríguez-Antona, C.; Abad-Santos F. Effect of the most relevant *CYP3A4* and *CYP3A5* polymorphisms on the pharmacokinetic parameters of 10 CYP3A substrates. *Biomedicines.* **2020**, *8*, 94. DOI: 10.3390/biomedicines8040094.
12. Oh, M.; Ghim, J. L.; Park, S. E.; Kim, E. Y.; Shin, J. G. Pharmacokinetic comparison of a fixed-dose combination versus concomitant administration of fimasartan, amlodipine, and rosuvastatin

using partial replicated design in healthy adult subjects. *Drug Des. Devel. Ther.* **2018**, *12*, 1157–1164. DOI: 10.2147/DDDT.S164215.
13. Abernethy, D. R. The pharmacokinetic profile of amlodipine. *Am. Heart J*. **1989**, *118*, 1100–1103. DOI: 10.1016/0002-8703(89)90834-X.
14. Talevi, A.; Quiroga, P.; Ruíz, M. E. *Biopharmaceutical Processes* [in Spanish]. Editorial de la Universidad Nacional de la Plata (EDULP), 2016, p 157.
15. Alvarado, A. T.; Muñoz, A. M.; Bendezú, M.; García, J. A.; Palomino-Jhong, J. J.; Ochoa-Pachas, G.; Chonn-Chang, A.; Sullón-Dextre, L.; Loja-Herrera, B.; Pineda-Pérez, M. In vitro biopharmaceutical equivalence of 5-mg glibenclamide tablets in simulated intestinal fluid without enzymes. *Dissolut. Technol.* **2021**, *28*, 1–12. DOI: 10.14227/DT280121PGC2.
16. Matiz, G. E.; Trujillo, M.; Pérez, D. A.; Baena, Y. In vitro evaluation of the interchangeability of different brands of diclofenac sodium tablets available in the Colombian market [in Spanish]. *Biomédica.* **2018**, *38*, 486–495. DOI: 10.7705/biomedica.v38i4.3988.
17. Evaluation list of counterfeit products and their alerts-DIRIS [in Spanish]; Dirección General de Medicamentos, Insumos y Drogas, Ministerio de Salud. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/ControlYVigilancia/ComercioIlegaal/ProductosFalsificados/Productos_falsificados_2019_Nacional_diris.pdf. (accessed Jan 19, 2021).
18. *Global Surveillance and Monitoring System for Substandard and Counterfeit Medical Products* [in Spanish]. Organización Mundial de la Salud, 2018.
19. *List of Generic Essential Drugs in the International Common Denomination* [in Spanish]. Resolución Ministerial No. 1097-2019/MINSA; Dirección General de Medicamentos, Insumos y Drogas, Ministerio de Salud, Nov 29, 2019. http://www.digemid.minsa.gob.pe/UpLoad/UpLoaded/PDF/Normatividad/2019/RM_1097-2019-MINSA.pdf. (accessed Jan 19, 2021).
20. Alvarado, A. T.; Muñoz, A. M.; Bendezú, M. R.; Palomino-Jhong, J. J.; García, J. A.; Alvarado, C. A.; Alvarado, E. A.; Ochoa-Pachas, G.; Pineda-Pérez, M.; Bolarte, M. In vitro biopharmaceutical equivalence of carbamazepine sodium tablets available in Lima, Peru. *Dissolut. Technol.* **2021**, *28*, 1–10. DOI: 10.14227/DT280221PGC2.
21. *The United States Pharmacopeia and National Formulary USP 35–NF 30*; The United States Pharmacopeial Convention, Inc.: Rockville, MD, 2012.
22. *The United States Pharmacopeia and National Formulary USP 37–NF 32*; The United States Pharmacopeial Convention, Inc.: Rockville, MD, 2014.
23. León, G.; Osorio, M.; Matiz, G. Comparative biopharmaceutical study of 500 mg acetaminophen tablets available in the Colombian market [in Spanish] *Rev. Cuba. Farm.* **2015**, *49*, 630–640.
24. Markopoulos, C.; Andreas, C. J.; Vertzoni, M.; Dressman, J.; Reppas, C. In-vitro simulation of luminal conditions for evaluation of performance of oral drug products: Choosing the appropriate test media. *Eur. J. Pharm. Biopharm.* **2015**, *93*, 173–182. DOI: 10.1016/j.ejpb.2015.03.009.
25. Dressman, J. B.; Berardi, R. R.; Dermentzoglou, L. C.; Russell, T. L.; Schmaltz, S. P.; Barnett, J. L.; Jarvenpaa, K. M. Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharm. Res.* **1990**, *7*, 756–761. DOI: 10.1023/A:1015827908309.
26. Krieg, B. J.; Taghavi, S. M.; Amidon, G. L.; Amidon, G. E. In vivo predictive dissolution: comparing the effect of bicarbonate and phosphate buffer on the dissolution of weak acids and weak bases. *J. Pharm. Sci.* **2015**; *104*, 2894–2904. DOI: 10.1002/jps.24460.
27. Stuart, A. V.; Clement, Y.; Sealy, P.; Löbenberg, R.; Montane-Jaime, L.; Maharaj, R. G.; Maxwell, A. Comparing the dissolution profiles of seven metformin formulations in simulated intestinal fluid. *Dissolut. Technol.* **2015**, *22*, 17–21. DOI: 10.14227/DT220115P17.