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Quality Control Parameters of Antihypertensive Medications Marketed in Eastern Ethiopia: Amlodipine Besylate and Enalapril Maleate Tablets

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ABSTRACT

Substandard medications have a negative impact on treatment outcomes. To get the desired therapeutic effect, drugs need to have the required pharmaceutical properties and the right amount of the active pharmaceutical ingredient. Thus, this study aimed to evaluate the quality control parameters of different brands of amlodipine besylate and enalapril maleate tablets marketed in Harar City, Eastern Ethiopia. Three brands of amlodipine besylate and enalapril maleate tablets were procured from community pharmacies in Harar City, Eastern Ethiopia. Weight variation, tablet breaking force, friability, disintegration, assay, and dissolution tests were carried out to evaluate quality control parameters of amlodipine besylate and enalapril maleate tablets. Corresponding results were compared with United States Pharmacopeia (USP) standards. All the brands of amlodipine besylate and enalapril maleate tablets met the USP specifications. Weight variation, breaking force, friability, drug content, and disintegration time for amlodipine besylate tablets ranged from –3.26–4.06%, 35.06–49.13 N, 0.11–0.49%, 97.98-99.97%, and 0.12– 0.68 minutes, respectively. Weight variation, breaking force, friability, drug content, and disintegration time for enalapril maleate tablets ranged from –2.97–5.93%, 77.86–156.49 N, 0.08–0.62%, 97.98-100.59%, and 2.63–9.03 minutes, respectively. The dissolution profiles of all brands of both antihypertensive medications were within the acceptable range. All brands of amlodipine besylate and enalapril maleate tablets available in Harar City fulfilled the USP requirements and could be used interchangeably in clinical practice.

Keywords: Quality control, amlodipine besylate, enalapril maleate, dissolution

INTRODUCTION

The global prevalence of hypertension is rising (*1*). In comparison to high-income countries, the burden of hypertension is significantly higher in low- and middle-income countries. Antihypertensive medications are the mainstay of therapy for the management of hypertension (*2*). The common pharmacological antihypertensive medication classes used as an initial treatment for hypertension are diuretics, calcium channel blockers (CCBs), and angiotensin-converting enzyme (ACE) inhibitors (*3*). From these latter two classes, amlodipine besylate and enalapril maleate are the common medications prescribed for patients with hypertension (*4, 5*).

Amlodipine besylate is a third-generation dihydropyridine class of long-acting CCBs. Chemically, it is 3-ethyl5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate (*6*). It is commonly used for the management of hypertension and other cardiovascular diseases such as stable angina, vasospastic angina, and coronary artery disease (*7–9*). It decreases blood pressure by selectively inhibiting calcium ion influx across cell membranes and subsequently relaxes vascular

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smooth muscles and dilates blood vessels (*8*). It is substantially transformed into inactive metabolites (approximately 90%) by hepatic metabolism. About 10% of the parent molecule and 60% of the metabolites are excreted in urine (*4*). Amlodipine besylate is freely soluble in methanol, poorly soluble in anhydrous ethanol, and slightly soluble in water and 2-propanol (*6*).

Enalapril maleate is a nonsulfhydryl ACE inhibitor. It is a prodrug that needs to be de-esterified via hepatic metabolism into its active form enalaprilat and monoethyl ester of enalapril (*10–13*). Chemically, it is (2*S*)-1-[(2*S*)-2-[[(1*S*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]propanoyl]
pyrrolidine-2-carboxylic acid (*Z*)-butenedioate (*6*). Enalapril maleate is commonly used to treat hypertension because it reduces peripheral vascular resistance, which in turn lowers blood pressure. It is also recommended for the treatment of congestive heart failure (*5, 11, 14*). Enalapril maleate and its metabolite are primarily excreted in urine (*10*, *11*). Enalapril maleate is freely soluble in methanol and poorly soluble in water (*6*).

To achieve targeted blood pressure, the quality of these medications must be assured. The quality of antihypertensive medications can be determined by in vivo or in vitro studies (*15*).

The quality of medicines is a key element in the safety and effectiveness of medications as well as in reducing total healthcare costs (*16*). Failure to comply with good manufacturing practices guidelines is a major cause of substandard quality of medicines. Additionally, problems in the supply chain and inappropriate storage conditions for medicines can also lead to quality problems (*17*). In low- and middle-income countries, around 10% of medical products are substandard or falsified (*18*).

In sub-Saharan African countries, the spread of substandard medications continues to be a substantial problem. In 10 of these countries, about 24.3% and 3.5% of generic and brand-name versions of antihypertensive drugs had poor quality, respectively (*19*). Numerous studies have also indicated a high frequency of substandard medications in Ethiopia (*20–22*).

Amlodipine besylate and enalapril maleate tablets are two widely prescribed antihypertensive medications in Ethiopia, so post-market quality control evaluation is indispensable. Therefore, this study aimed to evaluate the quality control parameters of different brands of amlodipine besylate and enalapril maleate tablets marketed in Harar City, Eastern Ethiopia.

METHODS

Amlodipine besylate and enalapril maleate reference standards were gifted from Sansheng Pharmaceutical PLC. Methanol (Blulux Laboratories Pvt, India), potassium dihydrogen orthophosphate (Loba Chemie Pvt. Ltd, India), disodium hydrogen phosphate (SCHEM Laboratory Chemicals, India), hydrochloric acid (HCl) (Loba Chemie Pvt. Ltd, India), and filter paper (0.45 µm pore size, GE Healthcare UK Ltd.) were used.

All available brands of amlodipine besylate 5-mg tablets (three brands, coded as AMa, AMb, and AMc) and Enalapril maleate 10-mg tablets (three brands, coded as ENa, ENb, and ENc) were procured from community pharmacies in Harar City, Eastern Ethiopia. All brands were obtained with their original packaging and the study was performed before product expiration dates (see details in Table 1).

The quality control parameters of the amlodipine besylate and enalapril maleate tablets were evaluated in vitro according to procedures stated in the *United States Pharmacopeia* (*USP*).

Weight Variation Test

From each brand of amlodipine besylate and enalapril maleate, 20 tablets were randomly selected (*23*). Then, each tablet was weighed individually on the analytical balance (RADWAG, USA), and the percentage of weight variation was calculated.

Table 1: Description of Amlodipine Besylate and Enalapril Maleate Tablet Brands Studied

Drug (dose)	Brand name (code)	Batch or lot no.	Manufacture date	Expiration Date	Manufacturer	Country of Origin
Amlodipine besylate (5 mg)	Amvasc (AMa)	BB129	02/2022	01/2024	East African Pharmaceuticals PLC	Ethiopia
	Klodip (AMb)	S98021003	11/2021	10/2024	Kopran Ltd	India
	Amlorine AMc)	91743	05/2021	05/2025	Remedica Ltd	Cyprus
Enalapril maleate (10 mg)	Envas (Ena)	D210122BX53	07/2021	06/2024	Cadila Pharmaceuticals PLC	Ethiopia
	Ena-Denk (ENb)	AA2	01/2021	01/2023	Denk Pharma	Germany
	Korandil (ENc)	91743	12/2020	12/2023	Remedica Ltd.	Cyprus

Thickness and Breaking Force Measurement

The thickness and breaking force of 10 randomly selected amlodipine besylate and enalapril maleate tablets from each brand were measured using a hardness tester (Toron Tech, Canada) (*24*). Values were presented as mean and standard deviation (SD); breaking force was expressed in Newtons (N).

Friability Test

Each brand of tablet under investigation had a unit weight of less than 650 mg, so a total tablet weight as close as possible to 6.5 g was used for the friability test. Tablets were randomly selected from each brand of amlodipine besylate and enalapril maleate, dedusted, weighed, and placed in the drum of a friability tester (Tianjin Tianda Tianfa Technology Co. Ltd, China) (*25*). The drum was adjusted to rotate at 25 rpm for 4 min, with a total of 100 rotations. Then, the tablets were removed, dusted, and weighed. The mean percentage of weight loss was computed for each brand.

Disintegration Test

From each brand of amlodipine besylate and enalapril maleate, six tablets were randomly selected and placed in the disintegration apparatus (Pharm Test, Germany) (*26*). The disintegration apparatus was filled with distilled water, and the temperature of the medium was kept at 37 ± 2 °C. The tablets were declared entirely disintegrated when all the particles passed through the wire mesh, and the time taken to disintegrate was recorded. The mean disintegration time and SD were computed.

Dissolution Test

Initially, an absorbance (at 239 nm) versus concentration calibration curve was constructed from different concentrations of amlodipine besylate reference standards (5, 10, 15, 20, and 25 µg/mL) prepared in a medium of 0.01 N HCl (*27*). A standard solution of enalapril maleate was prepared in different concentrations (2, 4, 6, 8, 10 µg/mL) using a phosphate buffer (pH 6.8) medium. Then, absorbance values were read at 215 nm by UV/Visible spectrophotometer (Jenway, UK). Lastly, the absorbance versus concentration calibration curve was constructed (*28*).

The dissolution test was carried out using a USP type 2 dissolution apparatus (paddle) (Pharm Test, Germany) (*27*, *28*). For amlodipine besylate, 500 mL 0.01 N HCl was used as a medium with a stirring rate of 75 rpm at 37 ± 0.5 °C, and paddles were covered with Teflon. In the case of enalapril maleate, the dissolution medium was 900 mL phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C at 50 rpm. The samples (5 mL) were taken at 5, 10, 15, 20, 25, and 30 minutes, and an equal volume of fresh dissolution media was replaced each time. Then, samples were filtered and diluted appropriately. Finally, the amount of drug dissolved was measured using UV/Visible spectrophotometer (Jenway, UK) at the wavelength of 239 and 215 nm for amlodipine besylate and enalapril maleate, respectively.

The dissolution apparatus was calibrated with a performance verification test using USP reference standard, and

all mechanical parameters (such as pump flow test, stirrer speed test, immersion depth test, centricity test, wobble test, and temperature test) were within permissible limits. The dissolution apparatus and UV/Visible spectrophotometer were in strict compliance with the USP, EP, and ISO requirements.

Assay

Twenty amlodipine besylate tablets were randomly selected from each brand and weighed. The tablets were ground, and 5 mg of amlodipine besylate was taken and added to a volumetric flask, then 5 mL of methanol was added and swirled. A sufficient amount of 0.01 N HCl was added to make 50 mL, then shaken by mechanical means until dissolved. The solution was then filtered and diluted by 0.01 N HCl to get 10 µg/mL. The absorbance of the solution was read at 239 nm (*27, 29*). For enalapril maleate, 20 tablets were randomly selected from each brand, weighed, and ground. Powder containing 2.5 mg equivalent weight of enalapril maleate was added to a volumetric flask. Then, phosphate buffer (pH 6.8) was poured up to 25 mL, shaken until it dissolved, and filtered. From this stock, 10 µg/mL was prepared by adding phosphate buffer (pH 6.8). The absorbance of the solution was read at 215 nm UV/Visible spectrophotometer (*28*). Both tests were performed in triplicate and drug contents were determined using a respective standard calibration curve.

Data Analysis

Statistical analysis was carried out using Origin Pro 2022 Software (OriginLab Corporation, USA). Data were expressed as percentages or mean ± SD.

RESULTS AND DISCUSSION

Assessing the quality of the drugs currently on the market is crucial for reducing the prevalence of substandard medications. A total of six brands were evaluated for quality parameters according to USP guidelines. Two brands (one amlodipine besylate brand and one enalapril maleate brand) were manufactured in Ethiopia, whereas the other four brands were imported from foreign countries (Table 1).

Weight Variation

Because accurate dosing has a significant association with the content of each dose unit, controlling tablet weights must be given great concern. AMb (222.23 ± 2.84 mg) and ENc (202.44 ± 4.92 mg) were found to have the highest weight among amlodipine besylate and enalapril maleate tablets, respectively (Table 2). Minimum variation in tablet weight is required as a quality attribute as it is key to the presence of a similar amount of active pharmaceutical ingredient (API) in each tablet. The percentage weight variation of all products tested was within the *USP* limit for tablets weighing 130–324 mg (*23*). This result is indicative of batch-to-batch uniformity in terms of the API content, which helps to ensure dose uniformity and consistent treatment outcomes.

Thickness and Breaking Force

Each brand of amlodipine besylate and enalapril maleate tablets had comparable thickness. Consistent tablet thickness is an important property, among other factors, that could play a substantial role in the adherence of patients to prescribed medications. Although thickness may be considered a physical characteristic that only affects the tablet's appearance, it additionally influences the number of pores in the compact, and hence, may affect the disintegration and dissolution profiles (*24*).

Tablets must be durable enough to endure the rigorous handling and movement encountered in the manufacturing process, across the medication distribution chain, and outside, by patients and other end users. The tablets must be also able to withstand the forces associated with manufacturing procedures like coating, packaging, and printing (*24*). A breaking force of about 4 kg (39.2 N) is regarded as the minimum criterion for an acceptable tablet (30). In lieu of this, all tablets, except AMa (35.06 ± 4.05 N), fulfilled the minimum requirement (Table 2). The breaking force is an unofficial test, and this brand is not considered to be poor quality.

Table 2: Pharmaceutical Properties of Amlodipine Besylate and Enalapril Maleate Tablets Studied

	AMa	AMb	AMc	ENa	ENb	ENc
Weight (mg)	133.86 ± 2.40	222.23 ± 2.84	204.89 ± 1.44	199.98 ± 1.85	169.32 ± 1.25	202.44 ± 4.92
Weight Variation (%)	–3.26 to 4.06	–1.63 to 2.55	–1.70 to 1.47	–1.44 to 2.06	–1.55 to 1.94	–2.97 to 5.93
Thickness (mm)	3.55 ± 0.03	3.21 ± 0.02	3.91 ± 0.02	3.00 ± 0.03	2.44 ± 0.02	3.51 ± 0.01
Breaking force (N)	35.06 ± 4.05	42.03 ± 3.86	49.13 ± 4.79	101.11 ± 5.06	77.86 ± 5.93	156.49 ± 18.89
Friability (%)	0.49	0.35	0.11	0.08	0.18	0.62
Disintegration time (min)	0.68 ± 0.04	0.12 ± 0.02	0.16 ± 0.03	3.68 ± 0.18	2.63 ± 0.21	9.03 ± 0.29
Drug content (%)	97.98 ± 0.26	99.24 ± 0.37	99.97 ± 0.47	98.81 ± 0.45	97.98 ± 0.26	100.59 ± 0.57

Values are expressed as mean ± SD or range. AMa, AMb, and AMc represent three brands of amlodipine besylate (5 mg) tablets, and ENa, ENb, and ENc represent three brands of enalapril maleate (10 mg) tablets.

Friability

AMc (0.11%) and ENa (0.08%) had the lowest percentage of friability among amlodipine besylate and enalapril maleate tablets, respectively (Table 2). According to the USP, a maximum mean weight loss of not more than 1.0% is considered satisfactory (*25*). Such tablets can withstand the various mechanical stresses to chipping and surface abrasion encountered during packaging, storage, shipment, and other steps in the distribution cycle.

Disintegration Time

According to the *USP,* all immediate-release tablets are expected to disintegrate within 15 minutes (*26*). All tested products had acceptable disintegration time, although the mean time varied between brands (Table 2). The average disintegration time ranged from 0.12–0.68 minutes and 2.63–9.03 minutes for amlodipine besylate and enalapril maleate tablets, respectively. It is possible to justify the appropriate usage of the disintegrating agent by noting that all tablet brands adhere to the standard specification for disintegration time.

Dissolution Profile

The dissolution profiles of various brands of amlodipine besylate and enalapril maleate are depicted in Figures 1 and 2, respectively. The specification for amlodipine besylate is at least 75% of the labeled amount of the drug should be dissolved within 30 minutes. Accordingly, all three brands of amlodipine besylate passed the dissolution test, as greater than 90% of the labeled amount was dissolved in 30 minutes (*27*). The dissolution properties of all investigated brands of enalapril maleate were also above the minimum value set for the drug, which is not less than 80% of the labeled amount in 30 minutes (*28*).

Drug Content

The drug content of amlodipine besylate and enalapril maleate tablets must be within 90–110% of the indicated amount (*27, 28*). The mean drug content of amlodipine besylate and enalapril maleate tablets ranged from 97.98–99.97% and 97.98–100.59%, respectively (Table 2).

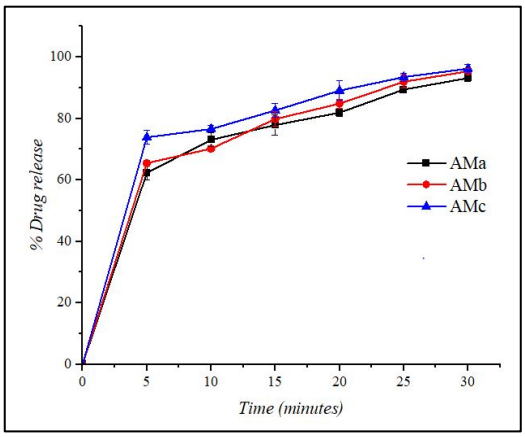

Figure 1: Dissolution profiles for three brands (AMa, AMb, AMc) of amlodipine besylate tablets.

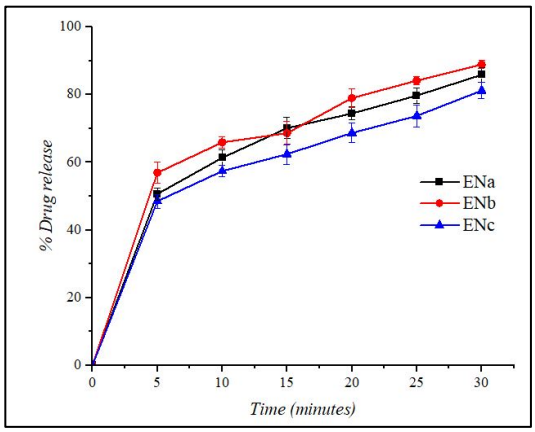

Figure 2: Dissolution profiles for three brands (ENa, ENb, and ENc) of enalapril maleate tablets.

CONCLUSION

All investigated brands of amlodipine besylate and enalapril maleate tablets available in Harar City, Eastern Ethiopia, fulfilled the USP requirements. In clinical practice, all investigated brands of amlodipine besylate and enalapril maleate tablets could be used interchangeably.

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DISCLOSURES

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