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COMPARATIVE *IN VITRO* EVALUATION OF DIFFERENT BRANDS OF NIFEDIPINE 20mg RETARD TABLET PRODUCTS MARKETED IN ADDIS ABABA, ETHIOPIA

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ABSTRACT

Nifedipine has been formulated and marketed as extended-release-film coated tablet. A certain degree of success has been achieved in reducing the incidence of adverse effects by the use of slow-release formulations such as nifedipine retard. The aim of the present study was to evaluate the physicochemical quality attributes and *in vitro* equivalence of six brands of nifedipine retard tablets available in different retail outlets in Addis Ababa, Ethiopia. After constructing the calibration curve, the *in vitro* drug release studies were carried out using USP type I dissolution apparatus at 100 rpm. The dissolution was done in a medium of 0.1N HCl containing 0.5% sodium lauryl sulfate for 12 hrs. All the tablets met the requirement for tablet weight uniformity. The mean crushing strengths of sample tablets ranged from 49.2 to 111.2 N. All the brands studied released more than 80% within 12 hours which is within the tolerance limit. However, the release profile revealed that five of the brands showed over 15% drug release at 1st hour except product F which released only 14.32%. In conclusion, all the brands of tablets had uniform thickness and good hardness. Despite all the brands had sustained the release for over 12 hours recommended for such formulations, five of them showed higher release in the first hour which may affect their *in vivo* performance.

Keywords: nifedipine, retard tablets, physicochemical properties, crushing strengths, *in vitro* drug release

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INTRODUCTION

Hypertension is a major public health problem world-wide with its attendant high rate of morbidity and mortality. Hypertension is a progressive disease that affects more than 1 billion people worldwide[1,2]. Reports showed that an estimated 639 million individuals had hypertension in developing countries in 2000 and this number is expected to rise to 1.15 billion by 2025[3].

The primary goal of antihypertensive therapy is to control blood pressure and reduce the long-term risk of cardiovascular morbidity and mortality. Different classes of medication are available for the management of hypertension[4,5,6]. Nifedipine [Dimethyl-2,6-methyl-4-(2-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate] (Fig 1) is a calcium channel blocking agent which is commonly employed in the management of systemic hypertension and angina pectoris[7].

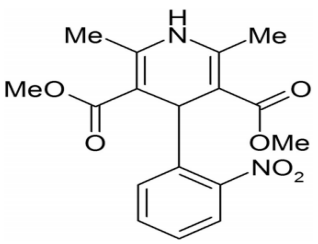

Figure 1: Chemical structure of nifedipine[7]

It has been demonstrated that the use of immediate-release nifedipine oral formulations have been

associated with rapid increase in nifedipine plasma concentration which results in increased heart rate and drug specific side effects such as flushing, dizziness, palpitation and reflex tachycardia. Accordingly, it is generally accepted that modified release formulations of nifedipine are the first therapeutic choice[1,4,6.8,9].

Sustained release nifedipine is prepared as an extended-release-film coated tablet. A certain degree of success has been achieved in reducing the incidence of such adverse effects by the use of slow-release formulations such as nifedipine retard[10,11,12].

Expiration of drug patents lead to several companies producing generic forms of drugs[13]. However, quality and performance of the generic versions of such drugs used in the management of chronic complications have been a source of debate among professionals and patients, particularly in the light of increasing circulation of counterfeited products and absence of strong regulatory systems in developing countries. The marketing of multisource drug products registered by national drug agencies in developing countries, with the view of improving health care delivery through competitive pricing, has an attendant problem of ascertaining their quality and interchangeability. As a result, health-care professionals sometimes pose questions whether these generics are equivalent to their original counterparts and whether patients are put at risk[14,15].

The formulation of a tablet drug product can have a significant effect on its physicochemical quality parameters such as hardness, weight variation, disintegration time, dissolution profile which may in turn affect the *in vivo* performance. Hence, the present study was carried out to evaluate the physicochemical quality and *in vitro* equivalence of six brands of nifedipine retard tablets marketed by different retail outlets in Addis Ababa, Ethiopia.

MATERIALS AND METHODS

Materials

Six different brands of 20 mg nifedipine retard tablets (Table 1) were purchased from retail outlets in Addis Ababa. All were film coated tablets except product C. Nifedipine reference standard was kindly donated by the Ethiopian Food, Medicine and Healthcare Administration and Control Authority (EFMHACA). Hydrochloric acid (BDH limited, Poole, England), HPLC grade methanol (Park Scientific Limited, UK), sodium lauryl sulfate, distilled water were used for the study. All chemicals used were analytical grade.

Table 1: Detailed description of products of nifedipine 20mg retard tablets included in the study

Brand Code	Manufacturer	Country of origin	Batch no	Expiry date
A	Cipla	India	GD61923	05/2019
B	Fabricadop	Germany	19021	08/2019
C	Cadila	India	G603016	06/2019
D	Remedica	Cyprus	69778	09/2019
E	E.I.P.I.Co	Egypt	1509228	10/2018
F	Cadila	India	D50025350	09/2017

Methods

Measurement of thickness

Ten tablets from each brand were taken and thickness was measured using sliding caliper scale (Nippon Sokutei, Japan). Results were expressed as a mean and standard deviation.

Crushing strength

Ten tablets were randomly selected from each brand product and the crushing strengths of the tablets were determined using hardness tester (Schleuniger, 2E/205, Switzerland). Each tablet was placed between two anvils and force was applied to the anvils, and the crushing strength that just caused the tablet to break was recorded. Results were expressed as a mean and standard deviation.

Weight variation

The weight variation test was evaluated by taking twenty tablets from each of the six brands, weighed individually with an analytical balance. The average weights for each brand as well as the percentage deviation from the mean value were calculated. Weight variation results were demonstrated as per USP (2013).

Disintegration time

Disintegration time test was carried out according to USP/NF (2013) specification. Six tablets were placed in a disintegration tester (CALEVA, G.B. Caleva Ltd., UK) filled with distilled water at 37±0.5°C. The tablets were considered completely disintegrated when all the particles are passed through the wire mesh and time was recorded.

Calibration curve for Nifedipine RS

Various concentrations of Nifedipine RS (17.5, 20, 25, 30, 35, 40, 45 and 50 µg/ml) were prepared in a medium of 0.1N HCl containing 0.5% sodium lauryl sulfate and methanol. Absorbances were measured at λ_{max} of 329 nm using a UV-Visible spectrophotometer (SOLAR Spectrofluorimeter, CM2203, Belarus). The values of absorbance were plotted against the corresponding concentrations.

In vitro drug release studies

The *in vitro* drug release studies were carried out using USP type I dissolution apparatus (ERWEKA, DT600, Germany) at 100 rpm. The dissolution was done in a medium of 900 ml 0.1N HCl containing 0.5% sodium lauryl sulphate for 12 hrs. The temperature was

maintained at 37±0.5 °C. Aliquot samples of 10 ml were withdrawn at pre scheduled intervals (1, 3, 4, 6, and 12 h) and replaced with an equal volume of fresh dissolution medium which was kept at 37±0.5 °C to maintain sink condition. Each filtered sample was analyzed for drug content at λ_{max} of 329 nm using a UV/Visible Spectrophotometer.

Statistical analysis

Origin 7 Software (OriginLab Corporation, MA, and USA) was used to statistically analyze the results. All the data measured and reported are averages of a minimum of triplicate measurements and the values are expressed as mean ± standard deviation.

RESULTS AND DISCUSSION

Tables 2 and 3 show some of the physicochemical characteristics of the nifedipine retard tablets studied. All tablets met the requirement (USP, 2013) for tablet weight uniformity and no tablet deviated from the average weight by more than 10% (samples A, C, D, E and F) and 7.5% (sample B). This compliance is important since the uniformity of dosage unit can be demonstrated by either weight variation or content uniformity study (USP/NF, 2013).

Table 2: Tablet weights of the nifedipine 20 mg retard samples used in the study

Tablet No	Weight (mg)					
	A	B	C	D	E	F
1	83.0	181.7	94.4	87.1	93.0	112.8
2	83.1	176.4	95.0	86.0	92.3	110.4
3	83.0	173.8	95.4	87.5	94.2	111.8
4	81.6	170.0	94.6	88.3	93.5	110.6
5	83.6	175.8	96.0	87.8	93.5	110.3
6	84.7	176.0	95.8	87.7	95.3	111.9
7	84.4	174.2	94.6	87.2	96.2	111.4
8	82.2	175.3	95.2	86.0	94.4	110.8
9	85.5	177.3	96.2	88.4	94.3	112.6
10	84.7	174.5	94.4	87.7	94.9	112.8
11	84.7	172.9	96.2	87.8	95.9	112.9
12	82.2	179.3	95.8	90.0	94.7	109.9
13	84.3	170.8	97.3	87.6	94.2	116.0
14	84.0	175.3	94.7	86.9	88.0	110.6
15	83.5	175.2	94.3	86.7	91.5	111.7
16	82.7	177.5	94.4	87.9	97.3	113.2
17	83.6	177.1	94.1	87.6	91.1	107.6
18	82.4	177.0	96.6	88.5	94.6	111.8
19	82.2	174.5	94.5	87.6	93.7	110.3
20	84.7	181.0	95.1	88.3	93.3	111.4

The tablet thickness ranged from 2.69 (product D and E) to 3.43 mm (product F). The mean crushing strengths of sample tablets ranged from 49.2 to 111.2 N. Sufficient tablet hardness is essential to ensure resistance to damage by handling, packaging and transportation. Tablet hardness of 4 kg is considered to be the minimum for a satisfactory tablet[12]; hence all tablets conformed to the necessary requirements. Maximum and minimum crushing strengths were observed from product D and A, respectively. Such differences in crushing strength may be resulted from different formulation and manufacturing technology.

Table 3: Some physicochemical characteristics of the nifedipine 20 mg retard samples studied

Brand	Tablet weight (mg)	Thickness (mm)	Crushing strength (N)	Disintegration time
A	83.51± 1.09	2.98 ± 0.02	49.2 ± 1.75	5min 10sec
B	175.78± 2.91	3.26 ± 0.06	84.5 ±2.72	45 sec
C	95.23 ±0.89	2.88 ± 0.05	72.7 ± 4.16	56 sec
D	87.63 ± 0.89	2.69 ± 0.02	111.2 ± 4.24	1min 50 sec
E	93.80 ± 2.02	2.69 ± 0.05	107.7 ± 4.62	3 hr 54 min
F	111.54 ± 1.69	3.43 ± 0.04	92.4 ± 3.20	> 5 hr

The disintegration time of the sample tablets showed great variation. Product B showed rapid disintegration time with only 45 seconds while with product F which remained intact even after 5 hrs. Such lowest disintegration time of product F may suggest slower dissolution rate.

Construction of Calibration Curve

The absorbance reading of nifedipine reference standard obtained was plotted against concentration (Figure 2). The linear regression equations obtained was Y = 0.01331X - 0.01291 (R^2 = 0.9992) in 0.1 N HCl containing 0.5% sodium lauryl sulfate and methanol where Y is absorbance and X is concentration in µg/ml.

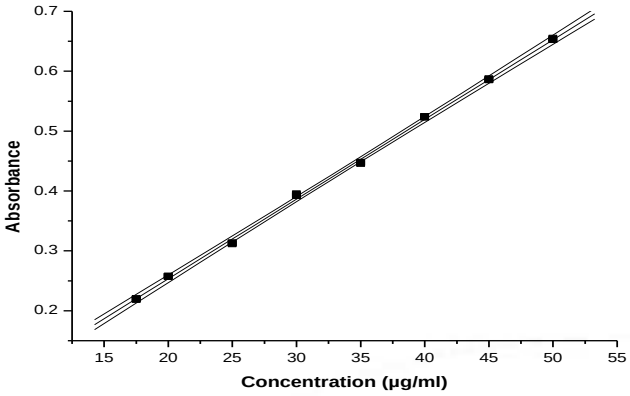

Figure 2: Standard calibration curve of nifedipine at λ_{max} of 329 nm in 0.1N HCl containing 0.5% sodium lauryl sulfate and methanol with upper and lower 95% confidence limits.

In vitro drug release

Bioequivalence studies are important to predict therapeutic equivalence between pharmaceutical equivalent test and reference products. *In vitro* dissolution studies have been recognized as important predictors of bioavailability for products on which formulation variables and processing parameters could have significant influence[16,17].

Of the tests that can be performed on tablets, the dissolution test is considered to be sensitive, reliable and rational for predicting *in-vivo* drug availability behavior[18].

The drug release characteristics of dosage forms are usually tested by means of pharmacopoeial test methods under highly standardized conditions. These very well established methods are widely used as a tool for quality control and for the optimization of dosage forms[9].

The result of drug release profile from the six brands of nifedipine retard tablets is illustrated in Figure 3. According to USP (2013), the acceptance limit for the amount of nifedipine released is given in Table 4. All the brands of nifedipine retard tablets studied released more than 80% within 12 hours which is within the tolerance limit. The release profile also revealed that five of brands showed more than 15% drug release at 1st hour while product F released 14.32% within the 1st hour. These results suggested that five of the studied brands (except F) exhibited higher initial drug release which may lead to dose dumping and compromise their therapeutic performance. Regarding the cumulative drug release within 4 hours, product F complied with USP dissolution tolerance limits (39%) but all others showed more release (>50%) than the stated amount within this period. Among all brands, product F had the least percentage release in the first 4 hours indicating its better retardant capacity than others.

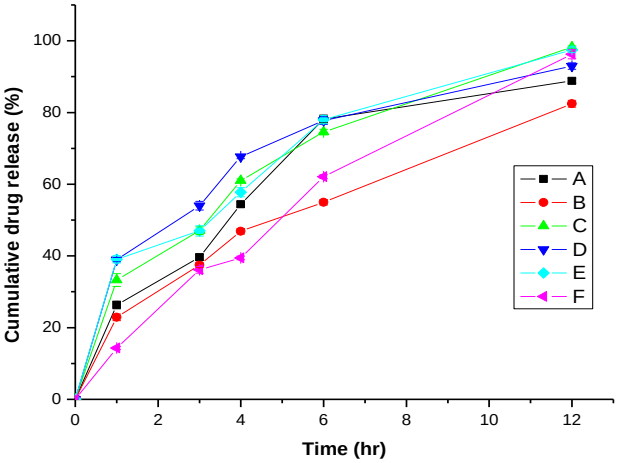

Figure 3: *In vitro* release profiles of nifedipine 20 mg retard tablets

Table 4: The cumulative percentage released of the labeled amount of nifedipine retard tablets at specified time (USP 2013).

Time (hr)	Amount released (%)
1	Not more than 15%
4	20%-40%
12	Not less than 80%

CONCLUSION

In the present study, 6 different brands of nifedipine 20 mg retard release tablets marketed in Addis Ababa were evaluated for different physicochemical properties. All the brands were found to have uniform thickness and weight and acceptable hardness. The results obtained were satisfactory and within the specified limits.

The first four brands were disintegrated within 15 minutes while product E and product F failed to disintegrate before 3 and 5 hours, respectively.

Based on the *in-vitro* dissolution studies, it was found that all brand products released more than 80% of the labeled amount within 12 hours in compliance with the USP tolerance limit. However, all brands except F released over 15% out of the acceptable monograph limit which may affect their *in vivo* performance. Similar pattern was observed up to 4 hrs where five of the brands released over 50% above the USP recommended tolerance limit and only product F could meet the requirement.

Therefore, the results of the present study revealed that all the studied brands meet monogram specification for most of the physicochemical quality parameters but most of them (except F) failed to meet the 1st and 4th hr USP *in vitro* dissolution tolerance limits which may affect the *in vivo* performance of these drugs.

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CONFLICTS OF INTEREST

Authors have declared that no conflicts of interest exist.

ABBREVIATIONS

EFMHACA: Ethiopian Food, Medicine and Health Care Administration and Control Authority

USP: United States Pharmacopeia

USP/NF: United States Pharmacopoeia/National Formulary

UV: Ultraviolet

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