African Journal of Biotechnology Vol. 9 (8), pp. 1274-1279, 22 February, 2010
Available online at http://www.academicjournals.org/AJB
ISSN 1684–5315 © 2010 Academic Journals

Full Length Research Paper

Physicochemical equivalence of some brands of Nifedipine retard tablets available in Nigeria

Okoye, E. I.* and Iwuagwu, M. A.

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Accepted 9 November, 2009

This research evaluated the physicochemical equivalence of some samples of Nifedipine 20 mg Retard Tablets available in Nigeria. Seven samples were randomly procured from various zones of the country and standard protocols applied to evaluate their tablet weight uniformity, dimensions, hardness, disintegration time, content of active Ingredient and *in vitro* drug release profile. Results showed that all the samples tested were chemically, but not physically equivalent. Although within each sample, compendial requirement for tablet weight uniformity was met, there were significant differences in the mean tablet weights, diameters and thickness of the samples studied ($p < 0.05$). Furthermore, tablet hardness and disintegration time varied much among the samples, but not within each sample. All the samples met the compendial requirement for content of active ingredient and released more than 80% of the drug within 4 h. It is therefore pertinent that manufacturers of this product be advised to formulate tablets that are equivalent in size, as different tablet sizes may impart negative psychological effects on clinicians and their patients when the need arises for switch over from one product to another, since the availability of particular products is never guaranteed at all times in Nigeria, a largely import dependent nation.

Key words: Nifedipine 20 mg Retard tablets, physicochemical equivalence, *in-vitro* drug release.

INTRODUCTION

In Nigeria, all the brands of Nifedipine 20 mg retard tablets available in the market, except one, are imported. As a result of the high cost of branded products, prescription and use of generic drug products is advocated in order that essential drugs would be affordable to all that need them.

However, unscrupulous importers, in order to ensure that their products compete commercially with other products, may sometimes compromise quality. As a result, healthcare professionals sometimes wonder whether those generics are equivalent to their original counterparts and whether patients are put at risk (Wiyada et al., 2002). Nifedipine is a calcium channel blocker used in the management of various cardiovascular diseases (Neal, 1995). It belongs to the dihydropyridine class of calcium channel blockers and is chemically known as dimethyl-1, 4-dihydro-2, 6-dimethyl-4- (2-nitrophenyl) pyridine-3, 5-dicarboxylate. It is light sensitive and its photo-reaction products (nitrosophenylpyridine and nitrophenylpyridine derivatives) possess highly diminutized pharmacological activity. It is a yellow crystalline powder, with melting point range of 171 – 175^{o}C (Al-Turk et al., 1989; Kennis et al., 2001; Martindale, 2002; USP/NF, 2002; BP, 2003).

The effects of nifedipine are evident within 30-60 min of an oral dose (Kennis et al., 2001). The elimination half-life for the immediate release formulation is 2-5h (CPS 2002). Apart from the relatively short half-life of the immediate release formulation, they have other short comings such as flushing, dizziness, palpitation and reflex tachycardia. These have necessitated the formulation of longer acting dosage forms and in some countries, the withdrawal of immediate release formulations from their markets (Brown et al., 1997; Minami et al., 2004; Emdex, 2006). In nifedipine retard, the rate of drug release is reduced by increasing particle size or forming insoluble crystals (MeRec, 2000).

Other applications of nifedipine are in the management of exercise induced asthma (Barnes et al., 1981), primary Raynaud syndrome (Kennis et al., 2001), prevention of

*Corresponding author. E-mail: ebypiaen@yahoo.com. Tel: +23408052742521.

Table 1. Identities of the Nifedipine 20 mg retard samples used in the study.

Code	Country of Origin	Shelf Life Status	Batch No.	NAFDAC No.
A	Nigeria	Not Expired	2676T	04-3161
B	India	Not Expired	MOI	
C	Israel	Not Expired	06E86	04-4499
D	India	Not Expired	K51025	04-7584
E	Austria	Not Expired	P-909	
F	Slovenia	Not Expired	31951054	04-0766
G	India	Not Expired	MNB-101	047943

atherosclerosis (Hirata et al., 2000), amelioration of endothelium injury in patients with systemic sclerosis (Allanore et al., 2004) and enhancement of the activity of anti-cancer drugs in colon cancer treatment (Yang and Friedlander, 2001).

MATERIALS AND METHODS

Materials

The samples (Table 1) studied were purchased from Lagos, Owerri, Onitsha, Ilorin, Suleja and Abuja. Nifedipine RS was purchased from Sigma-Aldrich Cheme GmbH, Germany. All other reagents were of analytical grade and water was double distilled.

Tablet weight, dimensions and hardness measurements

The weights of 20 tablets selected randomly from each sample were determined at room temperature using an electronic balance (Mettler Toledo B 154, Switzerland), while the dimensions (diameter and thickness) of 10 randomly selected tablets were measured using the Mitutoyo gauge (Model 10C-1012 EB Japan). The hardness values of another set of 20 tablets randomly selected from each sample were determined at room temperature using the Monsanto hardness tester (Monsanto Chemical Co. USA). The results reported are the means and standard deviations.

Disintegration time

The disintegration times of the tablets were determined in distilled water at 37 ± 0.5°C using the disintegration tester (Manesty, Model: MK 4, UK). Thereafter, all other tests were carried out under subdued light.

Calibration curve for Nifedipine RS

Various concentrations of Nifedipine RS (1.5, 2.5, 5.0, 10.0, 15.0, 20.0 and 25.0 µg/ml) were prepared in 0.1 M HCl. Their absorbances were read at 350 nm against 0.1 M HCl using a UV-Visible spectrophotometer (UV-160 A Shimadzu Corporation Japan). The values of absorbance were plotted against the corresponding concentrations. Data used in plotting the curve were mean values of at least duplicate determinations.

Content of active drug

Five tablets were randomly selected from each sample and finely crushed in an agate mortar. An amount of powder equivalent to 20 mg of nifedipine was dissolved in 50 ml of methanol in a 100 ml volumetric flask and shaken vigorously for 15 min. Thereafter, the flask was made up to volume with more methanol. The solution was filtered through a Whatman No 1 filter paper and 2.5 ml of the clear filtrate was pipetted into a 50 ml volumetric flask and made up to volume with more methanol. The absorbance of the solution was measured at 350 nm using methanol as blank. The content of active drug was calculated based on the absorbance of 10.0 µg/ml of Nifedipine RS in methanol at the same wavelength.

Dissolution rate

The dissolution rate study was carried out using the USP XXIII (1995) basket method (Erweka dissolution tester, Type DT 80, Germany), operated at 50 rpm. The dissolution medium was 750 ml 0.1 M HCl maintained at 37 ± 0.5ºC. Three tablets selected at random from each sample were used simultaneously for the study. A 5 ml volume of leaching fluid was withdrawn at various time intervals, filtered and appropriately diluted and its absorbance read at 350 nm against 0.1 M HCl as blank. The dissolution medium was replenished with fresh 5 ml aliquots at the same temperature after each sampling was done. The percentage of drug released was then calculated from the equation ($y = 0.0082x + 0.0022$) obtained from the calibration curve.

Statistical analysis

The Fisher test (F-test) was employed to test whether there were significant differences between the means (µ) of the diameters, thicknesses, or weights of the samples studied. The post-hoc test: Fisher's Least Significant Difference (FLSD) was carried out to locate the cause of the rejection of the null hypothesis (the means of the diameters, thicknesses, or weights of the tablets studied were equal) whenever it occurs.

$F_{calculated}$ = Treatment Mean Square / Error Mean Square

$FLSD = t_{critical} \sqrt{s^2 (1/ N_A + 1/ N_B)}$

where N_A and N_B are the sizes of the two treatment groups, s^2 is the pooled variance, estimated using the Error Mean Square term in the F-test and $t_{critical}$ is the critical t statistic associated with the experimental design (Jones, 2002). The $F_{calculated}$ values were evaluated using Microsoft Excel 2007 ANOVA: Single Factor Analysis Tool Pack.

RESULTS AND DISCUSSION

All the Nifedipine 20 mg Retard tablets studied were within their shelf lives (Table 1). Each had a labeled

Table 2. Tablet weights of the Nifedipine 20 mg retard samples used in the study (mg).

A	B	C	D	E	F	G
81.4	174.2	205.5	83.8	189.0	180.2	202.8
82.0	145.8	203.7	83.0	195.1	180.5	205.0
80.6	174.7	203.1	82.2	185.3	179.5	202.4
83.8	168.5	207.5	87.6	194.9	178.6	200.6
80.0	169.1	200.8	81.3	194.2	179.2	206.5
80.4	170.4	204.1	86.0	192.8	177.9	203.0
82.1	165.3	204.5	83.9	191.5	180.0	202.9
81.1	178.8	205.2	83.4	188.0	180.2	203.8
79.7	169.4	203.1	84.1	190.0	179.2	201.8
82.1	180.9	205.0	86.7	193.7	178.1	202.7
80.1	182.0	203.0	85.3	198.1	179.0	203.5
81.6	174.2	207.8	80.7	198.1	177.9	204.8
81.7	167.8	200.4	82.8	189.8	180.7	201.6
79.8	193.6	204.7	85.0	195.4	178.5	203.2
82.0	180.2	202.0	83.3	199.7	180.2	198.9
82.0	182.1	201.9	81.3	197.2	179.5	201.6
83.0	187.4	204.7	82.5	194.6	181.4	199.6
81.7	167.7	206.3	80.6	189.3	176.9	203.8
83.8	186.1	203.0	81.3	198.2	178.2	204.3
81.3	180.5	206.2	85.2	182.4	177.5	203.7
μ: 81.51	174.94	204.13	83.50	192.87	179.16	202.83
s: 1.191	10.290	2.023	2.007	4.630	1.197	1.812

μ = Mean weight; s = standard deviation.

Table 3. Some physicochemical characteristics of the Nifedipine 20 mg Retard samples studied.

Code	Tablet weight* (mg)	Tablet dimensions (mm)		Tablet hardness* (Kg)	Tablet disintegration time*(min)	Content of nifedipine (%)
		Diameter*	Thickness*			
A	81.51(1.191)	5.66(0.010)	3.10(0.018)	5.65(1.631)	7.91(1.197)	101.1
B	174.94(10.290)	7.95(0.019)	3.70(0.079)	4.95(0.945)	2.17(0.621)	104.3
C	204.13(2.023)	8.14(0.009)	4.07(0.020)	5.05(0.510)	1.08(0.132)	95.7
D	83.50(2.007)	5.64(0.004)	3.14(0.047)	5.70(0.571)	17.39(2.355)	98.9
E	192.87(4.630)	8.16(0.010)	3.79(0.066)	7.80(0.894)	7.06(0.822)	106.5
F	179.16(1.197)	8.20(0.008)	4.11(0.030)	7.50(0.607)	38.79(5.398)	102.2
G	202.83(1.812)	8.12(0.005)	3.80(0.042)	>11.00(-)	47.41(4.107)	94.6

* Standard deviation in parenthesis.

strength of 20 mg nifedipine as a slow release formulation. Of the seven (7) samples studied, two (2), B and E, were not registered with the National Agency for Food and Drug Administration and Control (NAFDAC). Only one (1) sample, A, was formulated in Nigeria.

Tables 2 and 3 show some of the physicochemical characteristics of the samples studied. The compendial requirement (BP, 2004) for tablet weight uniformity is met by all the samples in that not more than two of the individual weights from each sample deviated from the mean weight by more than 7.5% (Table 2). This compliance is important since the uniformity of dosage unit can be demonstrated by either weight variation or content uniformity study (USP/NF, 2003). These either reflect indirectly or measure directly the amount of drug substance in the tablet (Alderborn, 2002). The compliance within each sample notwithstanding, it is observable that the mean weight of the various samples varied widely and on application of ANOVA (Fisher's-test) and its least significance difference (LSD) post hoc test, significant differences were revealed, with the mean tablet weights (μ_w) related as follows: $\mu_{wA} = \mu_{wD} \neq \mu_{wC} = \mu_{wG} \neq \mu_{wB} \neq \mu_{wE} \neq \mu_{wF}$ ($p < 0.05$) (Tables 4c and 5). The test also revealed significant differences among the samples mean tablet

Table 4a. ANOVA results for tablet diameters.

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	87.05378	6	14.50896	137453.3	1.1229E-127	2.246407983
Within Groups	0.00665	63	0.000106			
Total	87.06043	69				

SS = sum of squares; df = degree of freedom; MS = mean square; F = calculated F- value.

Table 4b. ANOVA results for tablet thicknesses.

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	9.980789	6	1.663465	717.8456	5.34E-56	2.246408
Within Groups	0.14599	63	0.002317			
Total	10.12678	69				

SS = sum of squares; df = degree of freedom; MS = mean square; F = calculated F- value.

Table 4c. ANOVA results for tablet weights.

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	349280.56	6	58213.43	2878.133	3.9E-138	2.167423
Within Groups	2690.072	133	20.22611			
Total	351970.63	139				

SS = sum of squares; df = degree of freedom; MS = mean square; F = calculated F- value.

diameters and thicknesses, with the post hoc identifying that: $\mu_{dA} = \mu_{dD} \neq \mu_{dB} \neq \mu_{dF} \neq \mu_{dG} \neq \mu_{dE} = \mu_{dC} = \mu_{dG}$, $\mu_{tA} \neq \mu_{tB} \neq \mu_{tC} \neq \mu_{tD} \neq \mu_{tF} \neq \mu_{tE} = \mu_{tG}$ for mean tablet diameters and thicknesses respectively ($p < 0.05$) (Tables 4a, 4b, and 5). These differences in the tablet sizes (that is, weight, diameter and thickness) may actually have some negative psychological effects on clinicians and their patients since they could raise doubts on the general equivalence of the different brands of nifedipine 20 mg retard tablets available. Although the WHO Model Formulary (2002) advised that a patient be placed on a particular brand, probably due to pharmacokinetic and psychological reasons, in Nigeria where the availability of a particular brand for the patient concerned is never guaranteed at all times, it would be advisable that manufacturers of this product formulate tablets of equivalent sizes in order to assuage patients' worry regarding the identity and efficacy of the different brands because of the wide differences in tablet sizes.

Table 3 shows that the mean tablet hardness for the samples ranged from 4.95 to > 11.00 (Kg 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 (Rudnic and Schwartz, 2000). The disintegration times of the samples varied widely too and cannot be predicted from the tablet hardness values. This is not unusual since different manufacturers adopt different formulation techniques to manipulate the disintegration and release properties of nifedipine retard tablets (MeRec, 2000). The content of active ingredient in all the samples is within the range required by the USP/NF (2003), that is, not less than 90.0% and not more than 110.0% of the labeled content. Thus, all the samples studied are chemically equivalent.

The *in-vitro* drug release profile (Figure 1) depicts that all the samples released more than 80% of their labeled contents within 4 h. The profiles were different however, in that some products released up to 50% of their contents within the first 1 h, while three of them (D, F and G) did not. These differences in the patterns of release must have been caused by the manufacturers' choice of method of achieving reduction or delay in the rate of drug release (either increase in particle size or formation of insoluble crystals) (MeRec, 2000). The need to release up to 50% within 1 h is important because there is benefit in attaining a good blood pressure control level within 1 h and then maintaining it for at least the next 2 h (Kennis et al., 2001). On the whole, all the Nifedipine Retard tablets tested performed creditably and may perform even better *in vivo*, in the presence of some biosolvents that may enhance their release profiles.

Table 5. Fisher's LSD test on the Samples at 0.05 level (two tailed) with critical values = 0.03[d], 0.04[t], 2.81[w].

Diameter			Thickness			Weight		
Compar.	**Diff.**	**Signif.**	**Compar.**	**Diff.**	**Signif.**	**Compar.**	**Diff.**	**Signif.**
F – D	2.56	F≠ D	F – A	1.01	F ≠ A	C – A	122.62	C ≠ A
F – A	2.54	F ≠ A	F – D	0.97	F ≠ D	C – D	120.63	C ≠ D
F – B	0.25	F ≠ B	F – B	0.41	F ≠ B	C – B	29.19	C ≠ B
F – G	0.08	F ≠ G	F – E	0.32	F ≠ E	C – F	24.97	C ≠ F
F – C	0.06	F ≠ C	F – G	0.31	F ≠ G	C – E	11.26	C ≠ E
F – E	0.04	F ≠ E	F – C	0.04	F ≠ C	C – G	1.30	C = G
E – D	2.52	E ≠ D	C – A	0.97	C ≠ A	G – A	121.32	G ≠ A
E – A	2.50	E ≠ A	C – D	0.93	C ≠ D	G – D	119.33	G ≠ D
E – B	0.21	E ≠ B	C – B	0.37	C ≠ B	G – B	27.89	G ≠ B
E – G	0.04	E ≠ G	C – E	0.28	C ≠ E	G – F	23.67	G ≠ F
E – C	0.02	E = C	C – G	0.27	C ≠ G	G – E	9.96	G ≠ E
C – D	2.50	C ≠ D	G – A	0.70	G ≠ A	E – A	111.36	E ≠ A
C – A	2.48	C ≠ A	G – D	0.66	G ≠ D	E – D	109.37	E ≠ D
C – B	0.19	C ≠ B	G – B	0.10	G ≠ B	E – B	17.93	E ≠ B
C – G	0.02	C = G	G – E	0.01	G = E	E – F	13.71	E ≠ F
G – D	2.48	G ≠ D	E – A	0.69	E ≠ A	F – A	97.65	F ≠ A
G – A	2.46	G ≠ A	E – D	0.65	E ≠ D	F – D	95.66	F ≠ D
G – B	0.17	G ≠ B	E – B	0.09	E ≠ B	F – B	4.22	F ≠ B
B – D	2.31	B ≠ D	B – A	0.60	B ≠ A	B – A	93.43	B ≠ A
B – A	2.29	B ≠ A	B – D	0.56	B ≠ D	B – D	91.44	B ≠ D
A – D	0.02	A = D	D – A	0.04	D ≠ A	D – A	1.99	D = A

d = Diameter, t = thickness, w = weight.

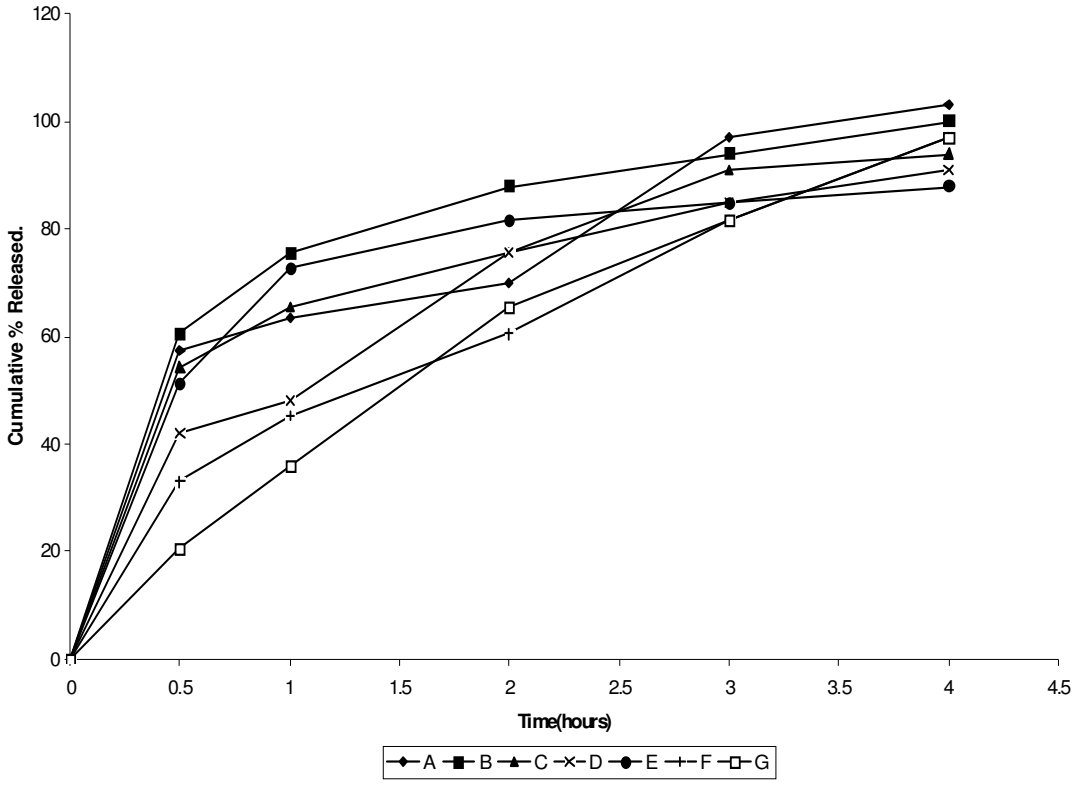

Figure 1. Dissolution profile of Nifedpine 20 mg retard tablets.

Conclusion

All the samples of Nifedipine retard tablets studied performed well *in vitro*. However, manufacturers of nifedipine retard tablets and other sensitive drugs should be advised to formulate products that are identical in size and colour so that patients, especially non-literate ones would not doubt the similarity in effectiveness of the different available brands.

REFERENCES

Alderborn G (2002). Tablets and Compaction. In: Aulton ME (Ed.), Pharmaceutics, the Science of Dosage Form Design; Longman Group UK; pp. 397-448.

Allanore Y, Borderie D, Lemorechal H, Ekindjian OG, Kahan A (2004). Nifedipine decreases sVCAM-1 concentrations and oxidative stress in systemic sclerosis but does not affect the concentrations of Vascular Endothelial growth factor or its soluble receptor I. Arthritis Res. Ther. 6: R309-R314.

Al-Turk W, Othman S, Majeed I, Murray M, Newton D (1989). Analytical Study of Nifedipine and its Photo-oxidized Form. Drug Dev. Ind. Pharm. 15(2): 223-233.

Barnes PJ, Wilson NM, Brown MJ (1981). A calcium Antagonist, nifedipine, modifies exercise induced asthma. Thorax. 36: 726-730.

British Pharmacopoeia (BP) (2003). Vol. II, Her Majesty's Stationery Office, London, p.1320

British Pharmacopoeia (BP) (2004). Vol. IV, Her Majesty's Stationery Office, London, p. A273.

Brown MA, McGowan LME, North RA, Walters BN (1997). Withdrawal of Nifedipine Capsules: Jeopardizing the treatment of acute severe hypertension in pregnancy? Med. J. Aust. 166: 640-643

Compendium of Pharmaceuticals and Specialties (CPS) (2002). The Canadian Drug Reference for Health Professionals, Canadian Pharmacists Association, Canada; p. 271.

Emdex (2006). The Complete Drug Formulary for Nigeria's Health Professionals. Obi CC (ed), Lindoz, Lagos; p. 166.

Hirata A, Igarashi M, Yamaguchi H, Suwabe A, Daiman M, Kato T, Tominaga M (2000). Nifedipine Suppresses Neo-Intimal Thickening by its inhibitory effect on Vascular Smooth muscle cell growth via a MEK-ERK pathway coupling with PyK2. Br. J. Pharmacol. 131: 1521-1530.

Jones DS (2002). Pharmaceutical Statistics. Pharmaceutical Press London; pp. 315-402.

Kennis DM, Robertson RM, Rebertson D (2001). Drugs Used for the treatment of myocardial Ischaemia. In: Hardman JG, Limbird LE (eds), Goodman and Gilman's The Pharmacological Basis of Therapentics, 10th ed., Mcgraw-Hills, New York; pp. 843-870.

Martindale (2002). The Extra Pharmacopoeia, 33rd ed., Royal Pharmaceutical Society, London; pp. 940-946.

MeReC Bulletin (2000). Modified release preparations. 11(4): 13-16.

Minami J, Numabe A, Andoh N, Kobayashi N, Itorinaka S,Ishimitsu T, Matsuoka H (2004). Comparison of Once-Daily Nifedipine Controlled Released with twice-daily Nifedipine retard in the treatment of essential hypertension. Br. J. Clin. Pharmacol. 57(5): 632-639.

Neal LB (1995). Antihypertensive Agents. In:Katzung BG (ed).Basic and Clinical Pharmacology, 6th ed., Appleton and Lange, Connecticut; pp. 147-170.

Rudnic ED, Schwartz JD (2000). Oral Solid Dosage Forms. In: Alfonso R Gennaro (ed.), Remjngton: The Science and Practice of Pharmacy, 20th ed., Lippincot Willians and Wilkins Inc., Philadelphia; pp. 858-893.

United States Pharmacopoeia 23/ National Formulary 18 (USP/NF) (1995). United States Pharmacopoeial Convention, Rockville; pp. 1942-1943.

United States Pharmacopoeia 263/National Formulary 21 (USP/NF) (2002). United States Pharmacopoeial Convention, Rockville; p. 1311.

United States Pharmacopoeia/National Formulary (USP/NF) (2003). United States Pharmacopoeial Convention, Rockville; p. 2227

WHO Model Formulary (2002). Couper MR, Melhta DK (eds). World Health Organization, Geneva; p. 236.

Wiyada A, Thitiwass S, Arunee P (2002). Pharmaceutical Quality of Nifedipine Soft Capsules Commercially Available in Thailand. J. Health Sci. 11(1): 1-8.

Yang JL, Friedlander ML (2001). Effect of Nifedipine in Metastatic Colon cancer with DNA Mismatch Repair gene defect. Lancet, 357: 1767-1768.