

Comparison of Two Marketed Nifedipine Modified-Release Formulations: An Exploratory Clinical Food Interaction Study

Dr. Meinolf Wonnemann¹; Dr. Barbara Schug¹; Maria Anschütz¹; Dr. Erich Brendel²; Prof. Gilberto De Nucci³; and Prof. Henning Blume¹

¹SocraTec R&D GmbH, Oberursel, Germany; ²Bayer Healthcare AG, Wuppertal, Germany; and

³SocraTec-Cartesius, Campinas, Brazil

ABSTRACT

Objective: The objective of this study was to compare the in vitro and in vivo characteristics of 2 nifedipine modified-release tablet formulations for once-daily dosing marketed in the European community, which were expected to be bioequivalent.

Methods: In vitro dissolution was tested at different pH values prior to the clinical part of the study. Either 1 tablet of a test formulation or of the reference formulation, both containing 30 mg nifedipine, were administered to healthy white male volunteers immediately after a high-fat breakfast in a randomized, open-label, 2-period crossover design. Plasma samples obtained over the subsequent period of 48 hours were analyzed using a validated LC-MS/MS method. Safety profile and tolerability of the study medications were assessed by analysis of adverse events obtained by vital sign measurements, electrocardiography, and clinical laboratory analysis.

Results: Twelve volunteers were enrolled (median age, 28.0 years [range, 21–42 years]; mean body mass index, 24.2 kg/m² [range, 19.3–27.0 kg/m²]). In vitro dissolution experiments revealed a significant pH dependency in drug release from the investigational tablets, while the reference tablets were found to have pH-independent dissolution. After oral administration of both tablet formulations in the fed state, marked differences in rate and extent of bioavailability were observed. Geometric mean of AUC_{0–last} (test, 504.21 h · ng/mL; reference, 361.28 h · ng/mL) was significantly higher for the test product, with a point estimate of 140% and a corresponding 90% CI of 121% to 161%. For the comparison of C_{max} values, geometric means were: test, 76.46 ng/mL; reference, 19.20 ng/mL, with a point estimate of 398% and a CI of 316% to 503%. Thus, a significant difference in rate and extent of bioavailability was observed between the 2 products.

Conclusions: Although both treatments were well tolerated by all volunteers, the test and reference tablets were found to have different pharmacokinetic properties when administered after a high-fat meal. (*Clin Ther.* 2008;30:online) Copyright © 2008 Excerpta Medica, Inc.

Key words: nifedipine, food interaction, bioavailability, modified-release products.

INTRODUCTION

Efficacy and tolerability of nifedipine for the treatment of hypertension and angina pectoris have been reported in numerous studies and publications.^{1–3} Initially, this calcium channel-blocking agent, a dihydropyridine derivative, was marketed as immediate-release soft-gelatin capsules containing the drug in solution. After oral administration of this formulation, the drug was absorbed rapidly and peak plasma concentrations were obtained within 30 to 60 minutes. Afterward, nifedipine was eliminated with a terminal t_{1/2} of 1.7 to 3.4 hours.^{1–9} Physiologic counter-regulations with sympathetic activation and an increase in heart rate were associated with the rapid increase of the drug concentrations in plasma. Consequently, modified-release tablet formulations were developed, which contain nifedipine as microcrystalline particles of a defined surface area. After oral administration of such formulations, peak plasma concentrations were observed at 1.6 to 4.2 hours and the apparent terminal elimination t_{1/2} increased to 6.0 to 10.8 hours due to a corresponding decrease of the absorption rate

Accepted for publication November 20, 2007.

Express Track online publication January 2, 2008.

doi:10.1016/j.clinthera.2008.01.001

0149-2918/\$32.00

© 2008 Excerpta Medica, Inc. All rights reserved.

(“flip-flop kinetics”).^{9–14} Accordingly, the dosing interval could be increased up to 12 hours. The goal of constant nifedipine plasma concentrations without substantial peak-to-trough fluctuations after once-daily oral administration could be achieved with the development of a gastrointestinal therapeutic system (GITS) formulation, which is based on an osmotic push-pull pump mechanism. These tablets consist of a 2-layered core surrounded by a membrane, which is permeable only for water but not nifedipine or other tablet constituents. One layer of the core contains the drug, the other one an osmotic system, which expands on water uptake. On top of the tablet an orifice has been laser-drilled through the semipermeable membrane. After oral administration, water from gastrointestinal fluid penetrates the membrane, causing a constant drug release over a period of ~16 to 18 hours.¹⁵ Considering a sufficiently long transit time through the gastrointestinal tract, this release characteristic results in an almost constant absorption rate over at least 24 hours and plateau-like plasma profiles of nifedipine without pronounced peak–trough fluctuations. As such, release occurs independently of pH value (within a range of 1.2–7.5),¹⁶ and drug delivery may also occur independent of food intake.^{17–20}

In previous years, several attempts were made to develop nifedipine formulations with pharmacokinetic characteristics similar to those of nifedipine GITS using a variety of galenic principles, including monolithic tablets with eroding matrices or multiple unit dosage formulations, such as pellets or mini-tablets. However, in most cases, the goal of independence from food intake could not be achieved.^{17–22} Significant food interactions were observed with several marketed products. Lack of robustness of drug release from these formulations (ie, considerable alterations of the drug-release characteristics), could be detected already in *in vitro* dissolution experiments under differing pH conditions reflecting the physiologic media in the gastrointestinal tract.^{17–22}

A new monolayer matrix nifedipine tablet* for once-daily administration has been registered by use of an abbreviated application procedure in the European Union (ie, referring to safety and efficacy data of the originator reference product[†]), which represents a GITS for-

*Trademark: Nifedipina Merck® (Merck Generics Italia, Valpharma, Italy).

†Trademark: Adalat OROS® (marketed in Italy as Adalat Crono) (Bayer SpA, Milan, Italy). OROS = oral osmotic therapeutic system.

mulation. After registration of the test product (license no. A033718026), initial *in vitro* experiments comparing both products concerning drug-release suggested differences in *in vivo* performance and bioequivalence of both products.²³ Thus, the aim of the present study was to compare the *in vitro* and *in vivo* characteristics of both nifedipine once-daily tablet formulations. The rate and extent of bioavailability were determined in the fed state (ie, the tablets were given immediately after intake of a high-caloric breakfast to reveal possible influences of food on the drug performance). Moreover, safety and tolerability were assessed by observation of adverse events and assessment of heart rate and systolic and diastolic blood pressure, electrocardiography (ECG), clinical laboratory parameters, and spontaneous reporting.

SUBJECTS AND METHODS

In Vitro Dissolution

In vitro dissolution characteristics of the study drugs were determined prior to the clinical study to determine a possible lack of robustness of the formulations. Therefore, tablets of each formulation were dissolved in 4 different buffer media (0.1 M hydrochloric acid, pH 1; acetate buffer, pH 4.5; phosphate buffer, pH 6.8; and phosphate buffer, pH 8) covering the entire pH range of the gastrointestinal tract under the addition of 1% sodium dodecyl sulfate to achieve sink conditions. Investigations were performed in a standard paddle apparatus²⁴ with a rotation speed of 100 rpm in vessels of 900 mL over the time range of 24 hours.

Clinical Study

The design of the study was open-label, randomized, and controlled and followed a 2-period crossover with single oral doses of either one 30-mg tablet of the test formulation or one 30-mg tablet of the reference formulation, with a treatment-free phase of at least 7 days to avoid any carryover effects in the second period. This exploratory trial was performed in 12 healthy volunteers without a formal sample size estimation as the number was considered sufficient to fulfill the objectives of the study. The investigation was performed in healthy males only as there have been no reports of gender-specific differences in nifedipine pharmacokinetics. Subjects were included according to specific inclusion and exclusion criteria, taking into account both participants' safety and optimal standardization of the study. Subjects with any clinically relevant lab-

oratory parameters out of range; clinically relevant findings in ECG or vital signs; existing cardiac, hematologic, hepatic, renal, gastrointestinal diseases or findings; clinically relevant diseases of the internal organs or central nervous system; severe allergies or hypersensitivities; or who had undergone a clinically relevant blood donation or participation in a clinical trial during the last months prior to the start of the study were excluded. Any medical disorder, condition, or history of such that would impair the subject's ability to participate or complete this study with a special focus on effect of absorption and metabolism led to exclusion of a subject. Furthermore, subjects were excluded if they had regular intake of alcohol ≥ 50 g pure ethanol per day or caffeine ≥ 250 mg/d, were active smokers, and/or had received any systemically available medication within 4 weeks prior to the intended first study drug administration unless, due to the corresponding terminal elimination $t_{1/2}$ values, complete elimination from the body for the drug and/or its primary metabolites could be assumed. Finally, drug or alcohol dependence and a positive virologic status (anti-HIV test, HBsAg test, or anti-HCV test) were to be excluded.

Prior to the start of administration of the investigational products a prestudy examination was performed to determine the general health status of the subjects. It included an anamnesis for medical history, a physical examination, determination of blood pressure and pulse rate (oscillometry using a manual noninvasive device), a 12-lead ECG, determination of hematologic and clinical chemistry parameters, and a urinalysis (the latter performed by a Good Laboratory Practices–certified central laboratory using common and quality-controlled standard methods for determination).

Hospitalizations started 12 hours before study drug administration in each period and lasted for 48 hours postdosing. Drug administration was performed under standardized conditions in an upright position with 200 mL tap water immediately after consumption of a high-fat breakfast served after an overnight fast (at least 10 hours). The breakfast consisted of ~150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively (1 fried egg [50 g], bacon [20 g], French bread [50 g] with margarine [20 g] and ham [40 g], 250 mL of whole milk with strawberry flavoring [15 g], and gelatin [100 g]).

No additional food (besides the high-fat breakfast) was allowed for at least 4 hours postdosing. Further standardized meals were served 4, 8, 12, 24, 28, and

32 hours postadministration, which had the same standardized composition in both periods. Water intake was standardized over 14 hours after every study drug administration (200 mL every 2 hours, 4 hours postadministration until 14 hours postadministration). Volunteers had to remain in a supine position for 4 hours after administration.

Blood sampling (5 mL blood per sample) for determination of nifedipine plasma concentrations was performed predose as well as 30 minutes, 1 hour, 1 hour and 30 minutes, and 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 30, 36, 42, and 48 hours postadministration. Real blood sampling times were documented and used for the evaluation. Samples were protected from daylight, frozen, and stored at $< -20^{\circ}\text{C}$.

Questioning for general well-being was performed in a nonleading manner. In addition to the questioning for general well-being at the prestudy examination and at the time of hospitalization, questioning for general well-being was also performed in the morning prior to the study drug administration as well as 1, 4, 8, 12, 24, 36, and 48 hours postadministration and at the poststudy examination. Blood pressure and pulse rate were measured in the morning prior to the study drug administration as well as 1, 2, 4, 8, 12, 24, 36, and 48 hours postadministration. Furthermore, the volunteers were asked to report any adverse events spontaneously, whether or not they occurred during confinement.

The entire trial was performed in accordance with the requirements of Good Clinical Practices and the current version of the Declaration of Helsinki.^{25,26} Each volunteer provided written informed consent, which could be withdrawn at any time. The design and procedures corresponded to recommendations of international guidelines. The study was approved by the Ethics Committee of the Faculty of Medical Sciences of the University of Campinas, Brazil.

Bioanalytics

Bioanalytical works were performed at Galeno Research Unit, Campinas SP, Brazil. A validated liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) method for the quantification of nifedipine in plasma samples was used. The analysis was validated and conducted in conformity with the study protocol and the US Food and Drug Administration Guidance for Industry: Bioanalytical Method Validation.^{27–29} Nifedipine and the internal standard nimodipine were extracted from human plasma by liquid/liquid

extraction using a mixture of diethyl ether/hexane (80/20 v/v). After the organic phase was removed, the extracts were reconstituted with a fixed volume of acetonitrile/water (50/50 v/v), which was analyzed by combined reversed-phase LC-MS/MS with negative photospray using a multiple reaction monitoring mode. All processes were carried out under light protection (yellow light, Osram L “62,” Osram GmbH, Munich, Germany).

The calibration range of the method was 0.1 (lower limit of quantitation [LLOQ]) to 500 ng/mL. Mean interassay accuracy of back-calculated concentrations for the calibration samples ranged from -9.4% to 5.0% and from -9.7% to 13.0% at the LLOQ. Quality-control samples in the concentration range of 0.3 to 400 ng/mL were determined with accuracies in the range of 93.1% to 103.0% and precisions in the range of 2.8% to 3.7% (interbatch) and 90.0% to 106.8% and 1.0% to 10.3% (inrabatch), respectively. Frozen samples were stored at -20°C. Stability data obtained (ie, postprocessing, freeze-and-thaw, short-term, long-term, master solution, and working solution stability tests) did not suggest any relevant degradation of the analyte at the temperatures and time periods tested. Measurement of plasma samples obtained was performed in a blinded manner (ie, the bioanalytical personnel were masked).

Pharmacokinetics and Statistics

All pharmacokinetic parameters were determined model-independently for each treatment phase using WinNonlin software program version 5.1 (Pharsight Corporation, Mountain View, California). Parameters were determined directly from measured concentrations. Actual sampling times were considered for pharmacokinetic evaluation. Area under the nifedipine concentration-time curve from dosing time to the last measurement time point with a concentration value above the LLOQ was calculated using the linear/log trapezoidal method, which used the linear trapezoidal rule up to C_{\max} , and afterward, the log trapezoidal rule for the remainder of the curve. The apparent elimination rate constant and corresponding elimination $t_{1/2}$ values were calculated using nonlinear regression on data points assessed to be located on the terminal phase of the concentration curves. The *lag time* parameter was defined as the time interval from dosing to the sampling time point showing the first quantifiable nifedipine concentration.

Analyses of variance (ANOVAs) were calculated for $AUC_{0-\text{last}}$, $AUC_{0-\infty}$, and C_{\max} after logarithmic transformation according to a multiplicative model using the factors subject, sequence, period, subject (sequence), and treatment. Ninety percent CIs were calculated for test:reference ratios using retransformation of the logarithmic data.

RESULTS

Study Population

A total of 12 volunteers were enrolled and finished the study according to the protocol without major protocol deviations. The median age was 28.0 years (range, 21–42 years), the mean weight was 70.2 kg (range, 58.5–80.0 kg), and the mean body mass index was 24.2 kg/m² (range, 19.3–27.0 kg/m²).

In Vitro Dissolution Tests

Mean profiles obtained from the in vitro dissolution tests are depicted in Figure 1. While the reference formulation was not found to have any significant alterations at different pH values of the media, differences in release profiles were found with the test product. After a lag time of nearly 2 hours the release characteristics of the reference product were linear over the time range up to 18 hours. Fifty percent was released after 12 hours; ~100% was reached after 24 hours. Differing pH of the medium did not lead to any changes. In contrast, nifedipine release from the generic (test) product was lowest at pH 4.5, with ~25% released after 12 hours and 50% after 24 hours. Surprisingly, the release at pH 1 was a bit higher in the end (~80% released after 24 hours). Neutral and alkaline pH values increased the release rate, with ~100% released after 10 and 12 hours at pH 8 and 6.8, respectively.

Pharmacokinetics and Statistics

Mean and individual nifedipine plasma concentration-time profiles are depicted in Figures 2 to 4. Pharmacokinetic results are given in Tables I and II; the statistical evaluation is presented in Table III.

After a lag time of ~1.5 hours, nifedipine plasma concentrations of the reference product constantly increased to a level of ~18 ng/mL after 6 hours. After that time point a plateau-like course (nearly 8–12 ng/mL) between 10 and 36 hours postadministration was observed. The remainder of the curve was characterized by a decrease to ~2 ng/mL after 48 hours. In contrast,

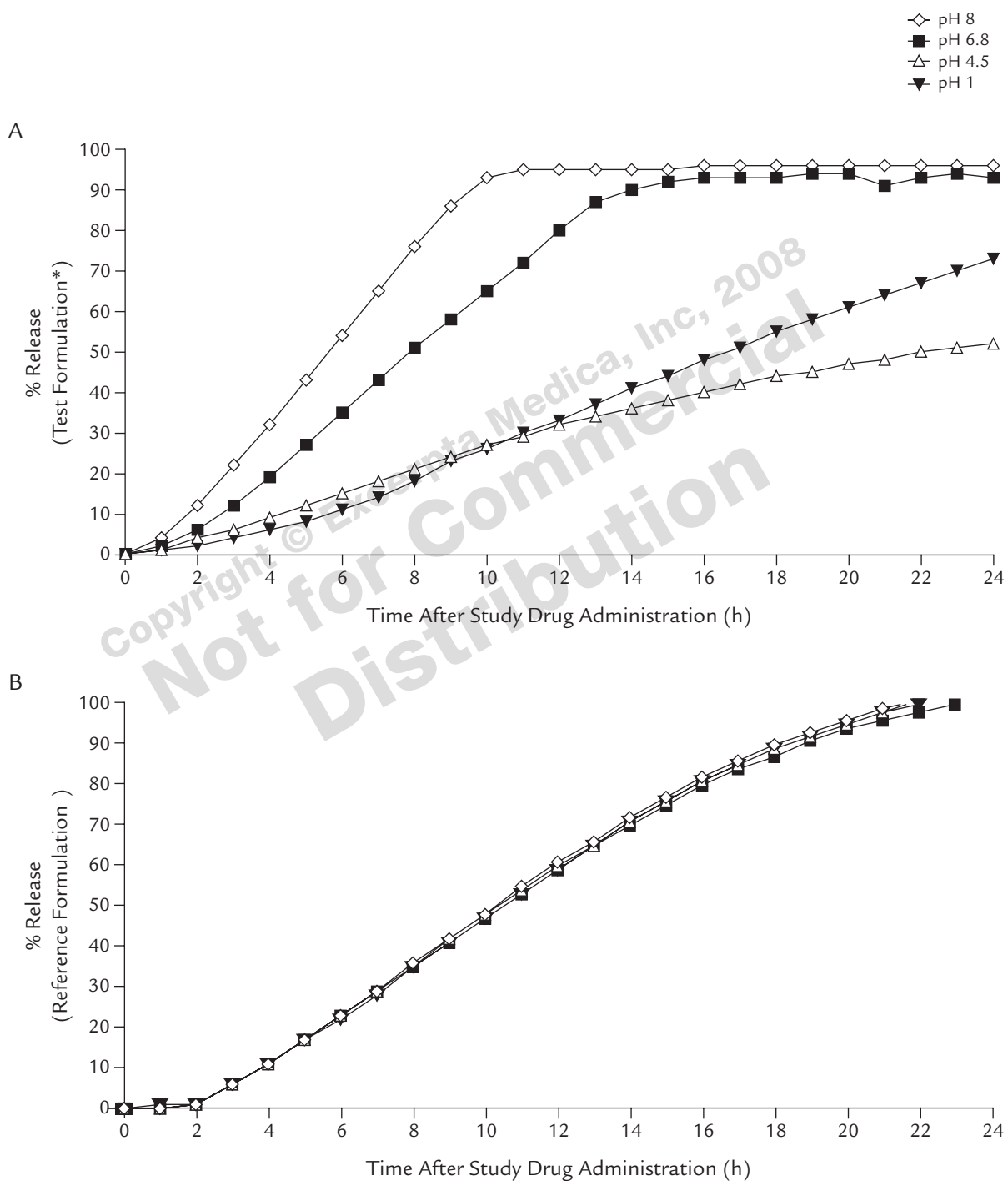


Figure 1. In vitro dissolution profiles of (A) test* (n = 6) and (B) reference† (n = 12) formulations of nifedipine 30 mg in 1% sodium dodecyl sulfate media (0.1 M hydrochloric acid, pH 1; acetate buffer, pH 4.5; phosphate buffer, pH 6.8; phosphate buffer, pH 8) determined in a standard paddle apparatus, 900-mL vessel with a rotation speed of 100 rpm. *Trademark: Nifedipina Merck® (Merck Generics Italia, Valpharma, Italy). †Trademark: Adalat OROS® (marketed in Italy as Adalat Crono) (Bayer SpA, Milan, Italy).

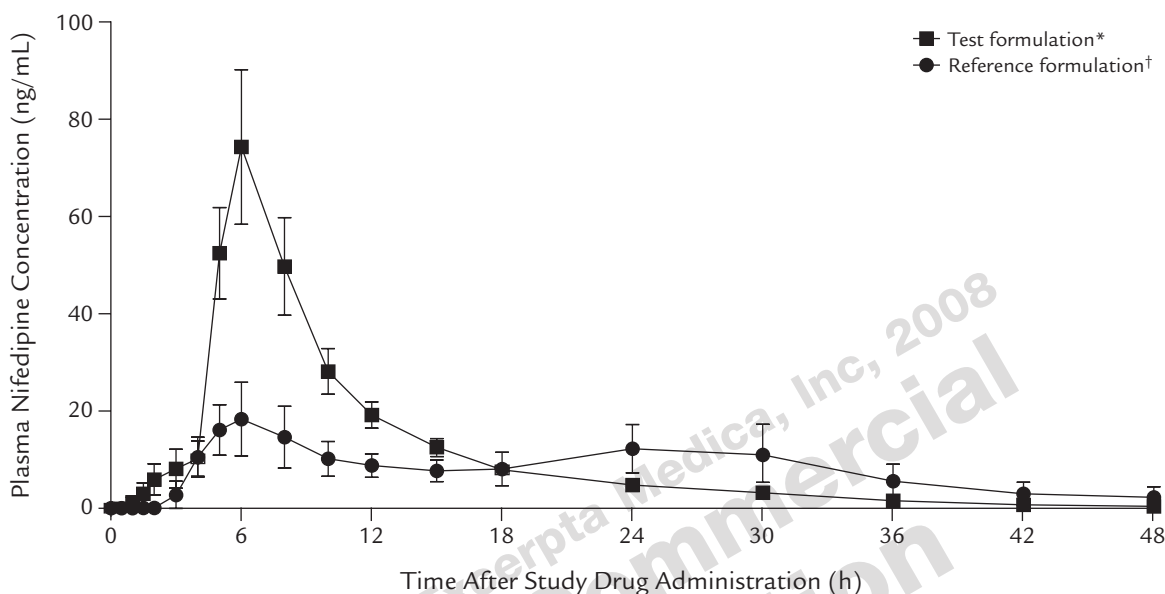


Figure 2. Mean (SD) plasma concentration–time curves of nifedipine 30 mg after oral, single-dose administration of test* and reference† formulations in 12 healthy white male volunteers following a high-fat breakfast. *Trademark: Nifedipina Merck® (Merck Generics Italia, Valpharma, Italy). †Trademark: Adalat OROS® (marketed in Italy as Adalat Crono) (Bayer SpA, Milan, Italy).

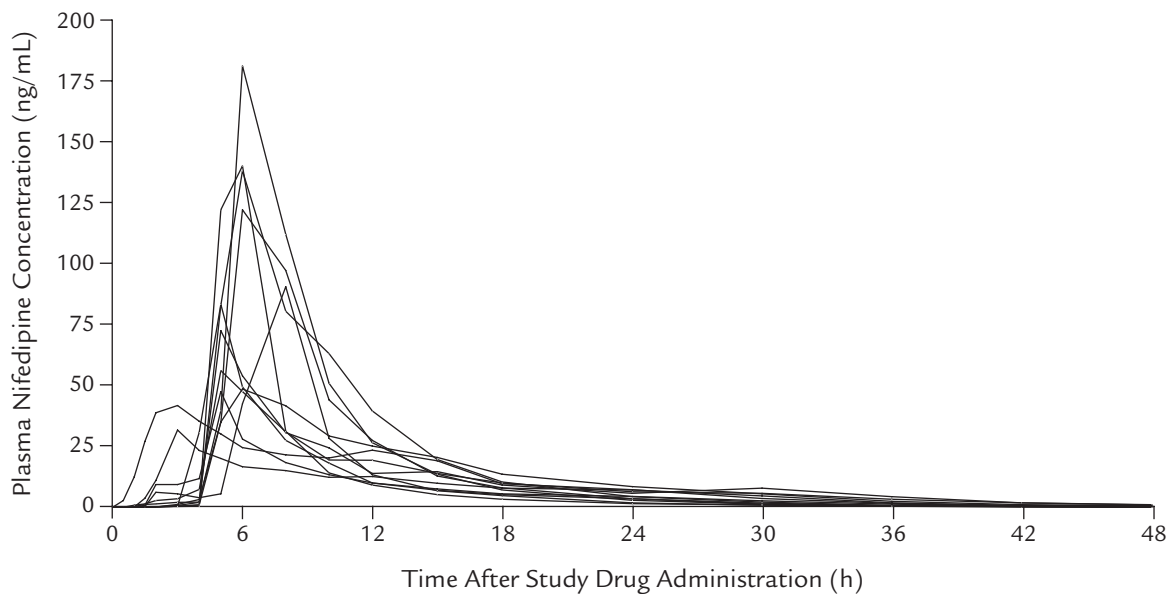


Figure 3. Individual plasma concentration–time curves after oral, single-dose administration of a test formulation* of nifedipine 30 mg following a high-fat breakfast in 12 healthy white male volunteers. *Trademark: Nifedipina Merck® (Merck Generics Italia, Valpharma, Italy).

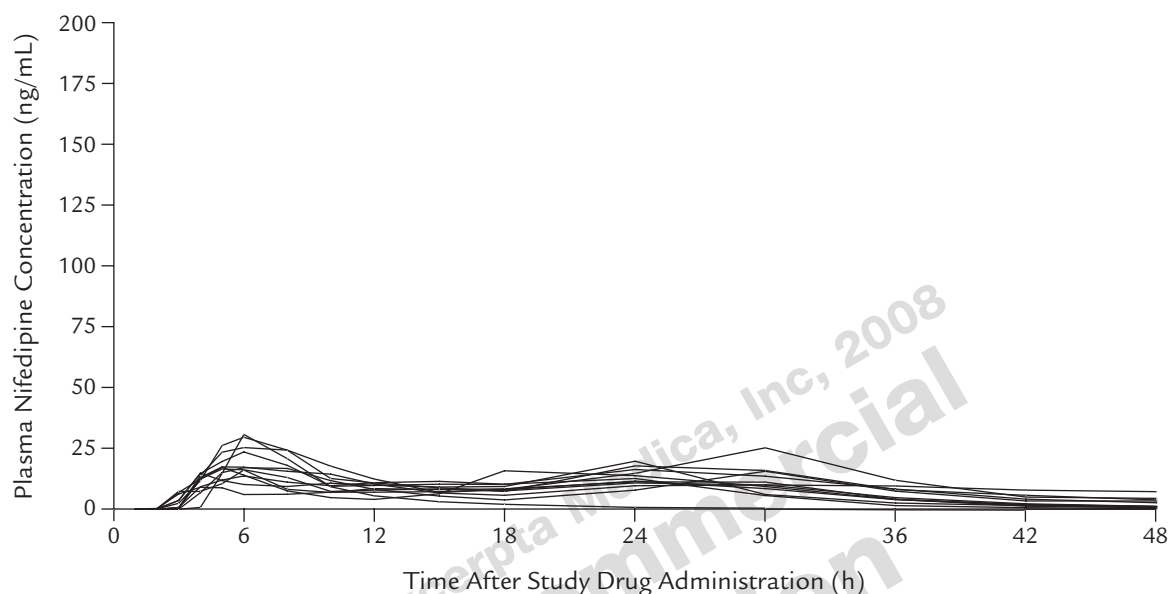


Figure 4. Individual plasma concentration-time curves after oral, single-dose administration of a reference formulation* of nifedipine following a high-fat breakfast in 12 healthy white male volunteers. *Trademark: Adalat OROS® (marketed in Italy as Adalat Crono) (Bayer SpA, Milan, Italy).

the mean curve of the test product did not suggest a pronounced lag time at the beginning, but an increase to nearly 10 ng/mL after 4 hours was followed by a steep rise to a maximum of the curve of ~75 ng/mL after 6 hours. Beyond that point the curve decreased to a level of nearly 20 ng/mL after 12 hours followed by a constant fall to a level of nearly 0.5 ng/mL after 48 hours. The relation of the maxima of the curves was ~4:1 for the test product versus the reference product.

The course of the mean curves was supported by the individual curves of both formulations. The highest maxima of the curves after intake of the test product was found in subjects no. 7, 8, and 9, with plasma concentrations of 181, 140, and 138 ng/mL, respectively. Thus, the individual ratios of the maxima following administration of the test product compared with the reference formulation were ~6:1, 9:1, and 5:1. One plasma concentration-time course following administration of the reference treatment was unexpected. Subject no. 10 was found to have concentrations close to the LLOQ 24 hours after intake compared with the corresponding mean concentration at 24 hours of 12.3 ng/mL.

The pharmacokinetic parameters derived underlined differences in the comparison of the plasma con-

centration profiles. Pronounced differences were found especially for AUC and C_{\max} values of the 2 formulations (ie, the parameters usually used to assess bioequivalence in confirmatory settings). The geometric mean of the $AUC_{0-\text{last}}$ of the test product was ~1.4-fold higher than that of the reference product; the mean of C_{\max} value was ~4-fold higher. A loss of modified-release characteristics was reflected by the differences in T_{\max} and MRT_{last} values. While the median T_{\max} values of both products were identical (6.00 hours), the marked difference in the range (3.00–8.00 hours for the test product; 5.00–24.08 hours for the reference product) suggests a distinctly different behavior in the in vivo release of nifedipine. Moreover, the median value of the MRT was almost twice as high for the reference product. A lag time already observed at the in vitro testing of the GITS system was also found in vivo. The reference product was found to have a lag time of ~1.5 hours, while that of the test product was 0.5 hour.

The determination of point estimates and 90% CIs for the parameters $AUC_{0-\text{last}}$, $AUC_{0-\infty}$, and C_{\max} confirmed the differences in the pharmacokinetic variables derived. The comparison of the 2 products found significantly higher $AUC_{0-\text{last}}$ and $AUC_{0-\infty}$ values for

Table I. Mean pharmacokinetic parameters of nifedipine after oral single-dose administration of test product* in 12 volunteers (30 mg nifedipine per treatment) following a high-fat breakfast.

Variable	Mean (SD)	Geometric Mean	CV%	Min	Median	Max
AUC _{0-∞} , h · ng/mL	-	508.54	29.76	309.77	499.99	814.37
AUC _{0-last} , h · ng/mL	-	504.21	30.19	306.27	489.95	812.97
C _{last} , ng/mL	-	0.34	74.68	0.12	0.36	1.11
C _{max} , ng/mL	-	76.46	54.11	31.70	77.90	181.00
t _{1/2} , 1/h	6.10 (0.76)	-	-	5.00	6.10	7.56
Lag time, h	0.50 (0.48)	-	-	0	0.50	1.50
T _{max} , h	5.43 (1.38)	-	-	3.00	6.00	8.00
MRT _{last} , h	11.87 (2.20)	-	-	8.38	11.87	14.74

MRT = mean residence time.

*Trademark: Nifedipina Merck® (Merck Generics Italia, Valpharma, Italy).

Table II. Mean pharmacokinetic parameters of nifedipine after oral single-dose administration of reference product* in 12 volunteers (30 mg nifedipine per treatment) following a high-fat breakfast.

Variable	Mean (SD)	Geometric Mean	CV%	Min	Median	Max
AUC _{0-∞} , h · ng/mL	-	396.42	45.25	160.31	358.02	906.94
AUC _{0-last} , h · ng/mL	-	361.28	30.49	158.68	350.45	598.73
C _{last} , ng/mL	-	1.36	95.41	0.21	1.24	7.23
C _{max} , ng/mL	-	19.20	30.31	11.60	17.60	30.80
t _{1/2} , 1/h	9.30 (9.91)	-	-	4.53	5.94	40.22
Lag time, h	1.54 (0.75)	-	-	0	1.50	3.00
T _{max} , h	10.34 (8.26)	-	-	5.00	6.00	24.08
MRT _{last} , h	20.07 (3.59)	-	-	9.75	21.03	23.31

MRT = mean residence time.

*Trademark: Adalat OROS® (marketed in Italy as Adalat Crono) (Bayer SpA, Milan, Italy).

the test formulation, with point estimates of 140% and 128%. The corresponding 90% CIs were 121% to 161% and 112% to 147%, respectively. The comparison of C_{max} values found a point estimate of 398% and a CI of 316% to 503%. Intraindividual variability for AUC was ~19% and nearly 32% for C_{max}.

Safety Profile

Adverse events observed during the study occurred in 5 of the 12 volunteers. In total there were 5 events, 3 with the test product and 2 with the reference product. All adverse events were of mild intensity and con-

sidered as not study drug related. Furthermore, none of the events were serious, and all resolved completely by the end of the trial. The most frequent adverse event was headache (4 cases). There were neither relevant changes in the clinical laboratory or ECG values nor marked changes in vital signs measured during the study periods. Thus, both treatments were considered as well tolerated.

DISCUSSION

According to the current European regulations, assessment of bioequivalence after administration of single

Table III. Point estimates and 90% CIs determined for the primary pharmacokinetic parameters of nifedipine; comparison of the test* versus reference† product following a high-fat breakfast.

Variable	Point Estimate, %	90% CI, %	CV _{ANOVA} , %
AUC _{0-last}	139.6	120.9–161.1	19.4
AUC _{0-∞}	128.3	111.7–147.3	18.7
C _{max}	398.2	315.5–502.6	31.5

*Trademark: Nifedipina Merck® (Merck Generics Italia, Valpharma, Italy).

†Trademark: Adalat OROS® (marketed in Italy as Adalat Crono) (Bayer SpA, Milan, Italy).

doses under fasting and fed conditions in comparison to the originator (reference) product is essential for an Abbreviated New Drug Approval of a generic (test) modified-release formulation to ensure appropriate efficacy and tolerability. Both products in this trial are currently approved and marketed in the European community. Consequently, the test product would be expected to exhibit a comparable *in vivo* performance in the fasted and fed states in comparison to the reference product.

No differences regarding tolerability were observed between the test and reference formulations in the present study. However, it should be considered that this study was only a single-dose exploratory trial with a limited number of healthy volunteers.

The 2 products were found to have marked differences in both *in vitro* dissolution characteristics and pharmacokinetics. *In vitro* dissolution testing found a differing behavior in drug release of the generic formulation with regard to pH changes of the dissolution media. In contrast, the reference product was not influenced by any of those changes but was found to have a lag time in drug release of ~2 hours. Neutral and alkaline pH values accelerated nifedipine release. In contrast, the release of the reference product was not significantly influenced by any of those changes.

Differences were observed in the nifedipine plasma concentration–time profiles of both formulations administered directly after a high-fat breakfast, which were underlined by the derived pharmacokinetic parameters and statistics. In the case of the reference

product the rate and extent of absorption are regulated by the push-pull system of the GITS and seemed to be unaffected by the intake of food. At least 4 clinical studies performed under both fasted and fed conditions in a similar setting revealed comparable profiles and pharmacokinetics after administration of the GITS formulation in the fed state.^{17–20} These trials investigated the pharmacokinetics of nifedipine by comparing various generic formulations (based on an enteric-coated principle, an erosion matrix system, or a mini-tablet formulation) with the GITS formulation. In all studies the GITS formulation was found to have a lag time of ~1.5 to 2 hours due to the underlying push-pull system of the tablet. However, the test product developed a “dose-dumping” effect after the intake of food. Besides a resultant higher extent of bioavailability, reflected by an increase in mean geometric AUC values, a significant increase in the geometric mean C_{max} value was noted. The relation of the latter was found to be 4:1 compared with the originator formulation. Moreover, in individual volunteers, this relation was even up to 9:1. This phenomenon went along with a loss in modified-release characteristics, visible by the resulting diminished MRT parameter. Concomitant food intake impairs the ability of the generic to release nifedipine in a regulated manner. The precise underlying mechanism for this “dose dumping” remains unclear, and experimental evidence for direct interferences between food and the formulation is not yet available. The study was not performed to assess clinical effects but to characterize bioavailability under fed conditions and, therefore, a normotensive population was chosen and blood pressure was not continuously monitored. According to the common understanding of bioequivalence assessment for different formulations, similar plasma concentration–time profiles are considered as a prerequisite for comparable efficacy and safety of 2 formulations containing the same drug substance.³⁰ The study found that significant differences especially in rate of bioavailability were observed for the comparison of both formulations under fed conditions. Therefore, the remarkable differences observed between the test and reference formulations suggest that comparable safety and efficacy cannot be ensured. Furthermore, for nifedipine, a direct relationship between absorption rate and antihypertensive effects has repeatedly been confirmed.^{10–12}

This study was performed in 12 male volunteers without a formal sample size estimation. Thus, a con-

firmatory assessment of bioequivalence was not possible. Assuming that the test formulation possesses pharmacokinetic characteristics similar to those of the reference formulation under fasting conditions, a remarkable food effect could be observed in every subject under treatment with the generic formulation, while it could not be observed under treatment with the reference product. A larger study in hypertensive patients is needed to evaluate the clinical impact of the current findings. Finally, the results of this investigation suggest that the 2 products cannot be regarded as interchangeable.

CONCLUSIONS

A significant difference in the *in vitro* dissolution characteristics of the 2 products investigated was observed, with a marked pH dependency of the generic product. Plasma nifedipine concentration-versus-time profiles suggest a “dose-dumping” phenomenon with the test product when taken after a meal. Relevant differences regarding rate and extent of bioavailability were found between the 2 products studied under fed conditions.

REFERENCES

1. Waters D. Related articles, links calcium channel blockers: An evidence-based review. *Can J Cardiol.* 1997;13:757-766.
2. Hedner T. Calcium channel blockers: Spectrum of side effects and drug interactions. *Acta Pharmacol Toxicol (Copenh).* 1986;58(Suppl 2):119-130.
3. Investigator's Brochure: BAY a 1040 (Nifedipine), version 7, December 2000.
4. Foster TS, Hamann SR, Richards VR, et al. Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects. *J Clin Pharmacol.* 1983;23:161-170.
5. Renwick AG, le Vie J, Challenor VF, et al. Factors affecting the pharmacokinetics of nifedipine. *Eur J Clin Pharmacol.* 1987;32:351-355.
6. Reitberg DP, Love SJ, Quercia GT, Zinny MA. Effect of food on nifedipine pharmacokinetics. *Clin Pharmacol Ther.* 1987;42:72-75.
7. Van Harten J, Burggraaf K, Danhof M, et al. Negligible sublingual absorption of nifedipine. *Lancet.* 1987;2:1363-1365.
8. Renwick AG, Robertson DR, Macklin B, et al. The pharmacokinetics of oral nifedipine—a population study. *Br J Clin Pharmacol.* 1988;25:701-708.
9. Brown GR, Fraser DG, Castile JA, et al. Nifedipine serum concentrations following sublingual and oral doses. *Int J Clin Pharmacol Ther Toxicol.* 1986;24:283-286.
10. Kleinbloesem CH, van Brummelen P, van de Linde JA, et al. Nifedipine: Kinetics and dynamics in healthy subjects. *Clin Pharmacol Ther.* 1984;35:742-749.
11. Donnelly R, Elliott HL, Meredith PA, et al. Nifedipine: Individual responses and concentration-effect relationships. *Hypertension.* 1988;12:443-449.
12. Brown M, Watts M, Mackenzie I, et al. Formulation of long acting nifedipine tablets influences the heart rate and sympathetic nervous response in hypertensive patients. *J Hypertens.* 2005;23(Suppl 2):S306.
13. Taburet AM, Singlas E, Colin JN, et al. Pharmacokinetic studies of nifedipine tablet. Correlation with antihypertensive effects. *Hypertension.* 1983;5:1129-1133.
14. Debbas NM, Jackson SH, Shah K, et al. The bioavailability and pharmacokinetics of slow release nifedipine during chronic dosing in volunteers. *Br J Clin Pharmacol.* 1986;21:385-388.
15. Chung M, Reitberg DP, Gaffney M, Singleton W. Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system: A controlled-release formulation of nifedipine. *Am J Med.* 1987;83:10-14.
16. Frishman WH, Sherman D, Feinfeld DA. Innovative drug delivery systems in cardiovascular medicine: Nifedipine-GITS and Clonidine-TTS. *Cardiol Clin.* 1987;5:703-716.
17. Schug BS, Brendel E, Chantraine E, et al. The effect of food on the pharmacokinetics of nifedipine in two slow release formulations: Pronounced lag-time after a high fat breakfast. *Br J Clin Pharmacol.* 2002;53:582-588.
18. Schug BS, Brendel E, Wolf D, et al. Formulation-dependent food effects demonstrated for nifedipine modified-release preparations marketed in the European Union. *Eur J Pharm Sci.* 2002;15:279-285.
19. Schug BS, Brendel E, Wonnemann M, et al. Dosage form-related food interaction observed in a marketed once-daily nifedipine formulation after a high-fat American breakfast. *Eur J Clin Pharmacol.* 2002;58:119-125.
20. Wonnemann M, Schug B, Schmücker K, et al. Significant food interactions observed with a nifedipine modified-release formulation marketed in the European Union. *Int J Clin Pharmacol Ther.* 2006;44:38-48.
21. Karim A, Burns T, Wearly L, et al. Food-induced changes in theophylline absorption from controlled-release formulations. Part I. Substantial increased and decreased absorption with Uniphyl tablets and Theo-Dur Sprinkle. *Clin Pharmacol Ther.* 1985;38:77-83.
22. Karim A, Burns T, Janky D, Hurwitz A. Food-induced changes in theophylline absorption from controlled-release formulations. Part II. Importance of meal composition and dosing time relative to meal intake in assessing changes in absorption. *Clin Pharmacol Ther.* 1985;38:642-647.
23. Brendel et al. Study no. PHC-PH-PD-P QCD F. Wuppertal, Germany: Bayer Healthcare AG; 2004.

24. Paddle-Apparatus (USP Apparatus 2), United States Pharmacopeia (USP) XXIII, Rockville, Md: 1995; 1791–1793.
25. European Medicines Agency, ICH Topic E6 (R1) Note for guidance on good clinical practice (CPMP/ICH/135/95), 2002.
26. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; Note of Clarification on Paragraph 29, Washington 2002; Note of Clarification on Paragraph 30, Tokyo 2004.
27. Draft guidance for industry: Bio-analytical method validation, US Dept of Health and Human Services, Food and Drug Administration, CDER, CVM, 2001.
28. Dos Santos Pereira A. The determination of Nifedipine in Human Plasma by LC-MS/MS using Nimodipine as the Internal Standard: GRU 10/04 v01 validation report, 2004.
29. Dos Santos Pereira A. The determination of nifedipine in human plasma by LC-MS/MS for the assay GDN 120/04. Analytical report, 2004.
30. Note for guidance on modified release oral and transdermal dosage forms: Section II (Pharmacokinetic and clinical evaluation). The European Agency for the evaluation of medicinal products, CPMP/EWP/280/96, 1999.

Address correspondence to: Dr. Meinolf Wonnemann, SocraTec R&D GmbH, Mainzerhofplatz 14, 99084 Erfurt, Germany. E-mail: meinolf.wonnemann@socratec-pharma.de