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# AN IN-VIVO BIOEQUIVALENCE STUDY OF A NEW NIFEDIPINE EXTENDED RELEASE DOSAGE FORM, 'OPTICAPS'

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## ABSTRACT

A single dose fasting cross over study was carried out in human volunteers comparing Nifedipin-Mepha 20 retard Opticaps® capsules to Adalat® retard tablets. Opticaps® is a newly developed release formulation containing an active ingredient in a "semi solid" matrix within a hard gelatin capsule. Pharmacokinetic variables were calculated from the nifedipine plasma concentration data and evaluated statistically. The results showed Nifedipin-Mepha 20 retard Opticaps® capsules to be bioequivalent to Adalat® retard in all respect. Primary parameters were calculated by fitting the mean plasma concentration data for a two compartment open first order absorption model with lagtime using the computer PCNONLIN program. The parameter's obtained were used to simulate blood levels for a multiple dose administration of 20 mg nifedipine every 12 hours.

## INTRODUCTION

Nifedipine, a dihydropyridine derivative has been successfully used for the treatment of hypertension and coronary heart diseases (1) because of its pharmacological action as a calcium ion antagonist. Because of its short half life (2), nifedipine is formulated as extended release tablets (Adalat® retard 20 mg). These tablets have been available in the European market for the past few years.

Since that time quite a few generic nifedipine extended release products have appeared in the same market place. These generic products, however, have not shown absolute bioequivalence to Adalat® retard (reference product) (3,4,5). This is demonstrated by reviewing comparative bioavailability studies that meet the present day criteria of bioequivalence for extended release dosage form products (6,7,8).

The objective of the present study was to investigate the bioequivalence of a new extended release formulation of nifedipine (Nifedipin–Mepha 20 retard Opitcaps® capsules to Adalat® retard 20 mg tablets).

'Opticaps®' is an oral dosage form, in which the active ingredient is incorporated in a 'semi solid matrix' (SSM) and is filled into a hard gelatin capsule. The semi solid matrix is composed of a mixture of approved and known tensides and polymers which upon heating form a uniform matrix (9). In the gastro–intestinal tract, the matrix release the drug at a controlled rate.

Besides the technological advantages in preparing a capsule of a light sensitive ingredient such as nifedipine, the Opticaps® technology shows a very low weight variation and a high dosing accuracy typical for liquid filling. These fillings are particularly useful for low dose active ingredients such as nifedipine.

## METHOD

Study design and Volunteers: The study was a complete random, two way, single dose, cross over design. Twelve male, non-smoking volunteers, in good health, between the age of 18 and 45 and a weight of 65 to 83 kg, were selected following a complete physical examination by a registered physician. The physical included ECG's, chest x-rays and medical histories. The study was however completed with 11 volunteers due to substance(s) in the plasma of one volunteer that interfered with the analytical methodology.

Test products and administration: The test product was Nifedipin-Mepha retard Opticaps® and the reference product was Adalat® retard 20 mg tablet.

Each product was administered with 180 ml water at 7.00 AM. The intake of food was prohibited 10 hours before and 4 hours after the dosing. Water was provided ad libitum until 1.0 hour pre-dose. Fluid intake was controlled and consistent for the first 4.0 hours.

Blood sampling: Sixteen blood samples (10 ml each) were obtained during each study phase from an anticubital vein using heparinized vacutainers.

The samples were drawn at 0 (base line), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 hours.

Analytical method: The blood samples were centrifuged immediately after collection and stored at −18°C for subsequent determination of nifedipine.

Nifedipine content in the plasma was determined using a GC coupled to an electron capture detector. The method was validated for linearity between a concentration range of 2.0 ng/ml to 200.0 ng/ml of nifedipine. The limit of detection was 2.0 ng/ml of nifedipine. Diazepam was used as the internal standard.

Pharmacokinetic analysis: Primary parameters were calculated by fitting the mean plasma concentration data to a two compartment open first order absorption model with lagtime (11,12) using the computer program PCNONLIN. The primary parameters obtained were used to simulate the blood levels for multiple dose administration fo 20 mg every 12 hours.

AUC (0–t) was calculated by trapezoidal rule, AUC (0–inf) was calculated as (AUC 0–t) + (Ct/Kel) where Ct is the last detectable plasma concentration. The elimination rate constant (Kel) was calculated from the terminal portion of the elimination phase. Peak plasma concentration (Cmax) and the time to reach the peak plasma concentration (Tmax), Half value duration (HVD) (11) and Mean Residence time (MRT) were calculated from the individual plasma concentrations.

Steady state plasma concentration Css) and the fluctuation index (FI) (11) were calculated from the multiple dose simulation results.

Statistical Analysis: All statistical analysis were carried out using SAS–GLM procedures.

Four–way analysis of variance (ANOVA) were carried out on all AUCs, Cmax, Tmax, Kel values and the plasma concentrations at each individual time point, in which subject, treatment, sequence and period were evaluated.

90 % asymmetric confidence intervals (2 one–sided t test) of all AUCs and Cmax were determined. Plots of residuals versus predicated and SAS univariate analysis were also carried out on these parameters.

## RESULTS AND DISCUSSION

The mean nifedipine plasma concentrations found upon administration of the two formulations tested are shown in figure 1.

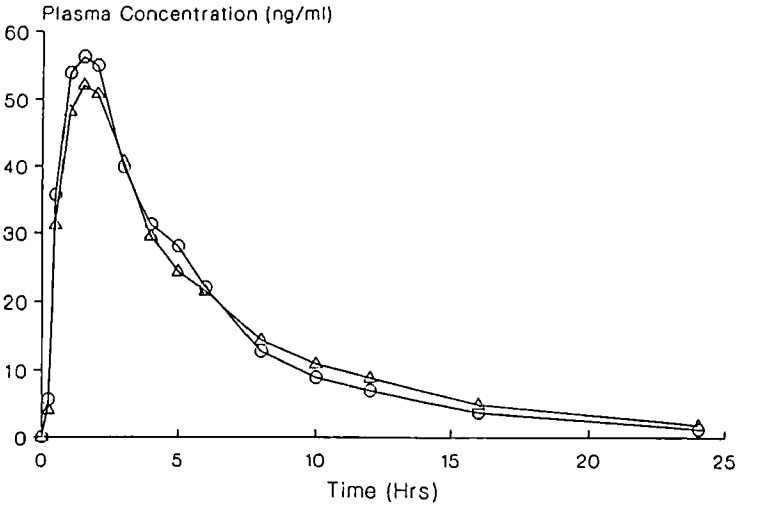


Figure 1 Mean nifedipine plasma concentration (ng/ml) after oral administration of Opticaps® and Adalat® retard tablets.
Key: (○) Opticaps®; (△) Adalat® retard tablets

Table I Pharmacokinetic parameters after oral administration of a single dose of 20 mg nifedipine as Opicaps® and Adalat® retard tablets

| Parameters | Opticaps | | Adalat retard | |
|---|---|---|---|---|
| | Mean | SDV | Mean | SDV |
| AUC (0–t) (ng Hr/ml) | 312.50 | 127.05 | 309.62 | 96.77 |
| AUC (0–inf) (ng Hr/ml) | 351.41 | 123.05 | 356.52 | 99.21 |
| Cmax (ng/ml) | 63.46 | 26.79 | 59.47 | 20.91 |
| Tmax (Hrs) | 1.82 | 1.17 | 1.91 | 1.51 |
| Kel (Hrs) | 0.133 | 0.046 | 0.144 | 0.066 |
| M.R.T. (Hrs) | 5.72 | 1.17 | 6.41 | 1.91 |
| H.V.D. (Hrs) | 3.74 | 1.15 | 3.64 | 1.14 |

Table II Statistical analysis of the pharmacokinetic parameters after single dose administration

| Parameters | Ratio % Opticaps/Adalat | Asymmetric 90 % C.I. |
|---|---|---|
| AUC (0–t) (ng Hr/ml) | 100.93 | 89.7 – 112.2 |
| AUC (0–inf) (ng Hr/ml) | 98.56 | 88.6 – 108.5 |
| Cmax (ng/ml) | 106.71 | 82.2 – 131.2 |

Table III Pharmacokinetic parameters of nifedipine multiple dose simulation from the data obtained after a single dose study

| Parameters | Opticaps | Adalat |
|---|---|---|
| Css (ng/ml) | 29.28 | 29.71 |
| Fluctuation Index | 1.54 | 1.41 |
| Cmax (inf. dose) (ng/ml) | 62.45 | 60.67 |
| Cmin (inf. dose) (ng/ml) | 7.96 | 10.39 |

The important pharmacokinetic parameters of the two formulations from the single dose study are summarized in table I and the results of the statistical analysis on these single dose parameters are shown in table II. The multiple dose pharmacokinetic parameters calculated from the simulated nifedipine plasma concentrations are shown in table III.

The nifedipine plasma concentrations following the ingestion of the two formulations, showed no statistical difference at any sampling time. The analysis of variance of the pharmacokinetic parameters – AUC (0–t), AUC (0–inf), Cmax, Tmax and the Kel, for the two formulations, also did not show any statistical difference. The 90 % asymmetric confidence intervals show that the test product lies well

within 80 to 120 % of the reference product with respect to the AUCs and the Cmax.

## CONCLUSION

From the results of the various analyses carried out on the data obtained from the single dose study, it is concluded that the Nifedipin-Mepha 20 retard Opticaps® formulation is bioequivalent to the Adalat® retard tablet in all respects.

The simulated steady state nifedipine plasma concentrations were found to be 29.28 ng/ml for the Opticaps® and 29.71 ng/ml for the Adalat® retard.

These data indicate that the Opticaps® formulation when used in a multiple dose study will very likely give the same results as the single dose study reported above. A multiple dose study is being planned and the result will be reported in a later paper.

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