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Pharmacokinetic Evaluation of Nicardipine Liquisolid Compact Tablets

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ABSTRACT

The aim of the present study is to compare the pharmacokinetics of nicardipine liquisolid tablets with its conventional tablets. 8 rats were taken, all the rats were having body weight approximately 200-260gr. Randomized Balanced Incomplete Block Design (BIBD) method was selected to determine pharmacokinetics of nicardipine liquisolid compact tablets. Blood samples were taken at predefined sampling points 0–24h after medication, and the plasma concentrations of nicardipine liquid solid compact tablets, conventional tablets were determined by high-performance liquid chromatography. The liquisolid compact tablets increased in C_{max} and AUC were observed, t_{max} occurred at 1.844 and 2.219 h with liquid solid compact tablets and conventional tablets. The area under the plasma concentration-time curve extrapolated to infinity AUC $(0-\infty)$ of liquisolid compact tablets was shown more than its conventional tablets. This research showed that formulation of nicardipine liquisolid compact tablets shown increase of bioavailability.

Keywords: nicardipine, pharmaco kinetics, rats, liquisolid compact tablets, study design, bio availability.

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INTRODUCTION

Nicardipine is a dihydropyridine calcium-channel blocking agent used for the treatment of vascular disorders such as chronic stable angina, hypertension, and Raynaud's phenomenon[1-2]. However, the drug bioavailability is very limited (15 – 40 %) to short elimination half-life(about 1 h), and like other dihydropyridine derivatives, its standard formulation undergoes rapid absorption and extensive biotransformation in the liver, which oftener results in significant fluctuations in plasma concentrations[3].To attain a prolonged therapeutic effect and a reduced incidence of side effects, sustained/controlled release formulations of NC have been developed to maintain a suitable plasma level for a long period of time, with minimal frequency of daily administration. NC microspheres using acrylic polymers[4], and NC microcapsules with ethyl cellulose as a coating material have been prepared for this purpose[5]. Cyclodextrin (CDs), cyclic oligosaccharides with a hydrophobic central cavity that provide microenvironment for appropriate sized non-polar molecules are also strong candidates for achieving drug controlled release at the desired level[7-8].These carriers have been widely applied as multi functional. These excipients are modifying drugs physical, chemical and biological properties[6]. The structure of nicardipine hydrochloride is showed in Figure 1. In this present study we are adding tween-80, avicel, aerosil. These excipients does not change chemical, biological property of drug and enhance bioavailability of nicardipine.

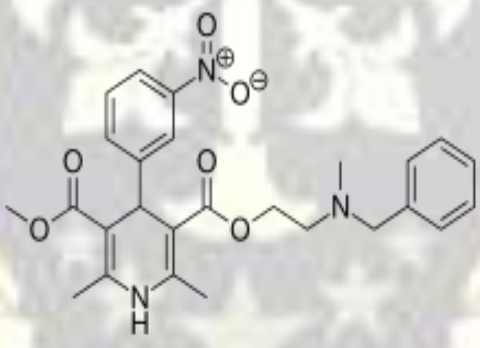

Figure 1:Chemical structure of Nicardipine

MATERIAL AND METHOD

Materials:

Nicardipine was gifted by Natco laboratories Hyderabad, tween80, avicel pH 102 and aerosil were purchased from E.Mecrk (India), crosspovidone, Methanol for HPLC grade were purchased from SD fine chemicals (India).

Preparation of liquisolid tablet and conventional tablet:

Accurate amount (20 mg) of drug was suspended in the liquid vehicle (tween-80; 200 mg) in a mortar using pestle, then the calculated amount of the carrier material (avicel; 512 mg) was added

with continuous mixing till homogenous wet mix is obtained. The coating material (aerosol; 57 mg) was then added to the wet mix with gentle mixing. Finally, each liquisolid formulation was blended with disintegrating agent (crosspovidone 64 mg), glidant and lubricant. From this blend we are taken dose according body weight of rat.

Then blend was finally compacted using flat faced punches using rotary tablet compression machine.

Instrument conditions of HPLC:

A model of waters alliance 2695 XE separation module with a UV-detector and an online degasses was mixed and empowers chromatography software to be used in prediction of samples. Chromolith TM Performance RP-C_{18} (50mm×4.6mm, 5µ) column is used. Mobile phase consist mixture of methanol and water at the ratio of 13:87 v/v was delivered at the rate of 1.0 ml/min. The injection volume was 10µL.

Preparation of calibration curve:

The calibration curve was performed with standards of the final concentrations of 2.5, 5, 10, 20, 50, 100, 150, 200, 300, 400 and 500 ng/ml in selective animal plasma. Diethyl stilbestrol used as internal standard. The calibrated standard graph was plotted by taking concentration vs peak area ratio (PAR) were given in figure. 2

Study design:

For these *In vivo* bioavailability studies, suitable 08 rats were selected, for which standard diet was procured all over study period because of diet should not interfere on absorption of given dosage form and they were not medicated earlier to studies. All the rats were having the body weight approximately of 200-260g.

To proceed the above studies, Randomized Balanced Incomplete Block Design (BIBD) method was selected and predicted the bioavailability of optimized formulation, as well as was compared both the bioavailability of reference and optimized formulation. As per the above formulation animal dose is approximately equivalent to 20.51mg/kg.

In this method each selective animal (rat) will not receive more than two formulations in entire studies and give at least one formulation in each study period. So a single rat can receive each formulation not more than of four times and pair of each rat receive alternatively same combination of formulations in each study period. Hence these total studies were designed to two successive study periods and between the each study period a proper wash out period was maintained. Finally the calculated amount of drug was selected from the both formulation divided in fine powder state. From this equivalent weight of drug was taken and suspended in solution

containing 0.25% of carboxyl methyl cellulose. There after depend up on body weight of each rat, required dose was measured and administered through oral feeding tube into the rat and collect the all blood samples at predetermined time intervals up to 24 hrs from rat retero orbital vein. i.e., 0.0,0.25,0.50,1.00,1.50,2.00,2.50,3.00,6.00,12.00 and 24.00 hrs. After collecting samples, separation of plasma done by centrifugation process at 5000 rpm for 5min and stored under frozen condition till the analysis was performed. Above the samples were determined by High performance liquid chromatography, from the obtained peak area values, plasma concentrations were determined and graph was plotted by taking plasma concentration on Y-axis and time on X-axis. From the concentration values obtained AUC (0-t) and all other possible pharmacokinetic parameters such as C_{max}, t_{max}, half-life etc, were calculated for each formulation and for each subject.

Study design of Nicardipine Liquisolid compact formulations

KFO: optimized formulation

KFP: Nicardipine markated formulation

Table: 1 *In vivo* Study design of Nicardipine HCl

Subject (Rat)	Study Period	
	I	II
1001	KFO	KFP
1002	KFP	KFO
1003	KFO	KFP
1004	KFP	KFO
1005	KFO	KFP
1006	KFP	KFO
1007	KFO	KFP
1008	KFP	KFO

Pharmacokinetic data analysis:

Non-compartmental model of Winnonlin version 5.3 were used in estimation of plasma concentration Nicardipine hydrochloride with respective definite time intervals for every successive periods of rats. From this provided data, basic principles of pharmacokinetic characteristics are predetermined for the development of bioavailability studies, such as measured maximum plasma concentration followed by each treatment (C_{max}), The area under the plasma concentration respect to the time curve from (t_0) time zero to the measurable last concentration (AUC_{0-t}), The area under the plasma concentration and time curve from time zero to infinity ($AUC_{0-\infty}$) and time to approach maximum plasma concentration (T_{max}).

RESULTS AND DISCUSSION

The drug-plasma concentrations obtained from the bioavailability study for test (optimized) and reference (marketed) products were analyzed in each subject by HPLC method and calculated the basic pharmacokinetic parameters such as C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{½}$. The plots of comparative individual plasma concentrations of test and reference products in each subject were shown in figure 3 to 10. Plot of comparative mean plasma concentrations of test and reference products was shown in figure: 11. Comparisons of relative bioavailability for test and reference products were given in Table 2.

All the obtained values were reported in terms of arithmetic mean (SD) of maximum concentrations (C_{max}) for both the test and reference products were found 1725.466 (302.54) and 1536.265 (251.65) ng/ml, the maximum time required to reach peak plasma concentration (T_{max}) for the samples of test and reference values were recorded 1.844 ± 0.516 and 2.219 ±0.619 hours, the amount of drug retained for absorption (AUC_{0-t}) for the test and reference products were given 1488.098 (242.101) and 1450.378 (257.422) ng.h/ml, as well as $AUC_{0-\infty}$ for the test and reference products were noted 1629.404 (296.234) and 1581.535 (307.192) under fasting conditions.

These studies were also extended for bioavailability of both the test product with reference product was confined by the calculation of 90% confidence interval for the In-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Nicardipine (table 3). The 90% confidence intervals for area under the plasma concentration respect to the time (AUC_{0-t}) were 97.31-108.87, maximum concentration of drug plasma (C_{max}) were found to be 99.70-114.31, and for $AUC_{0-\infty}$ were noted 97.17-109.75. The recorded and calculated confidence intervals were looking the bioavailability criteria (within the limit of 80 to 125) with respect to the rate and extent of absorption for Nicardipine hydrochloride under fasting conditions.

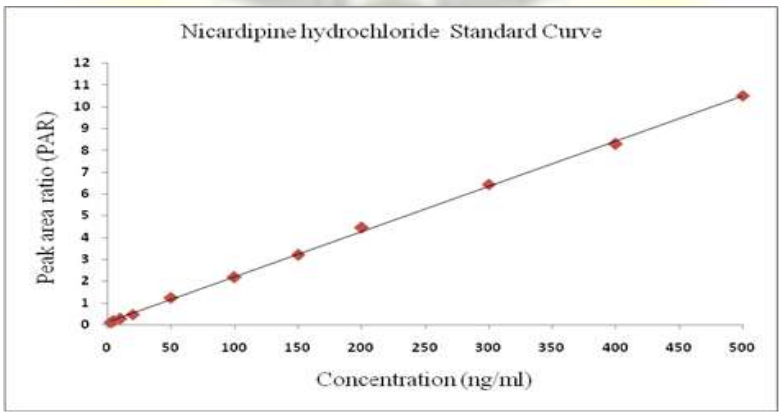

Figure: 2 Standard curve for Nicardipine hydrochloride

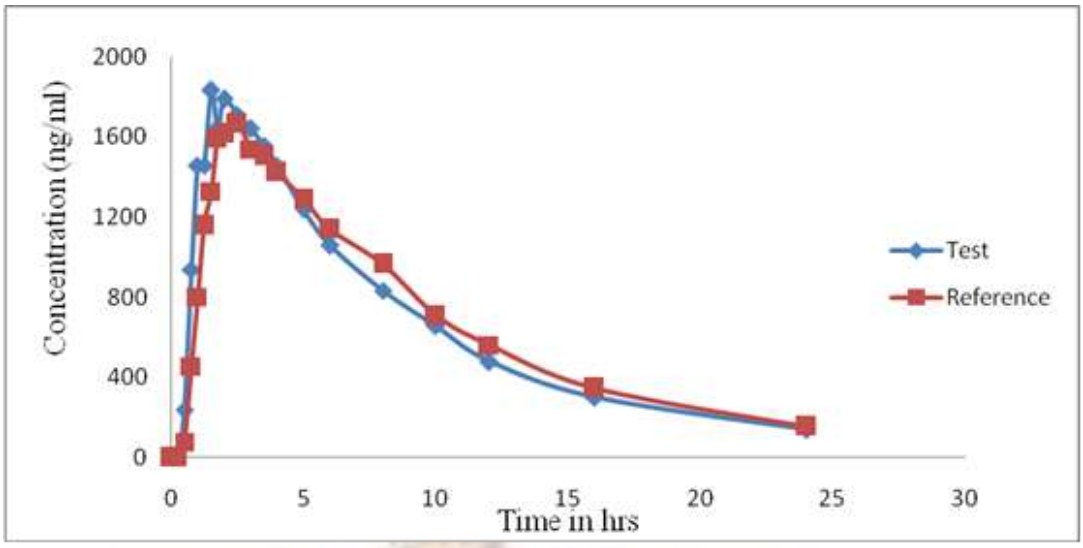

Figure: 3 Individual plasma concentrations

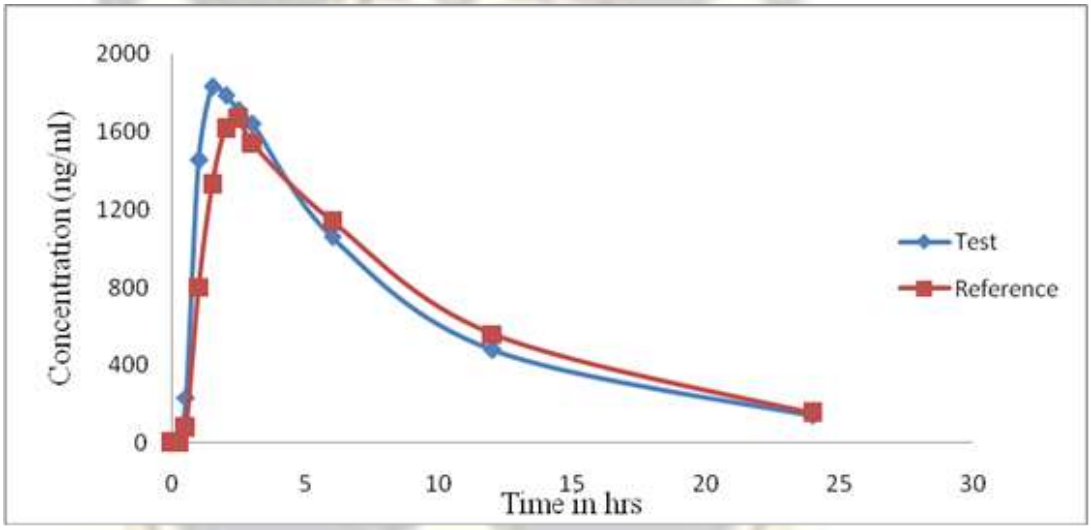

Figure: 4 Individual plasma concentrations of test and reference in subject 1002

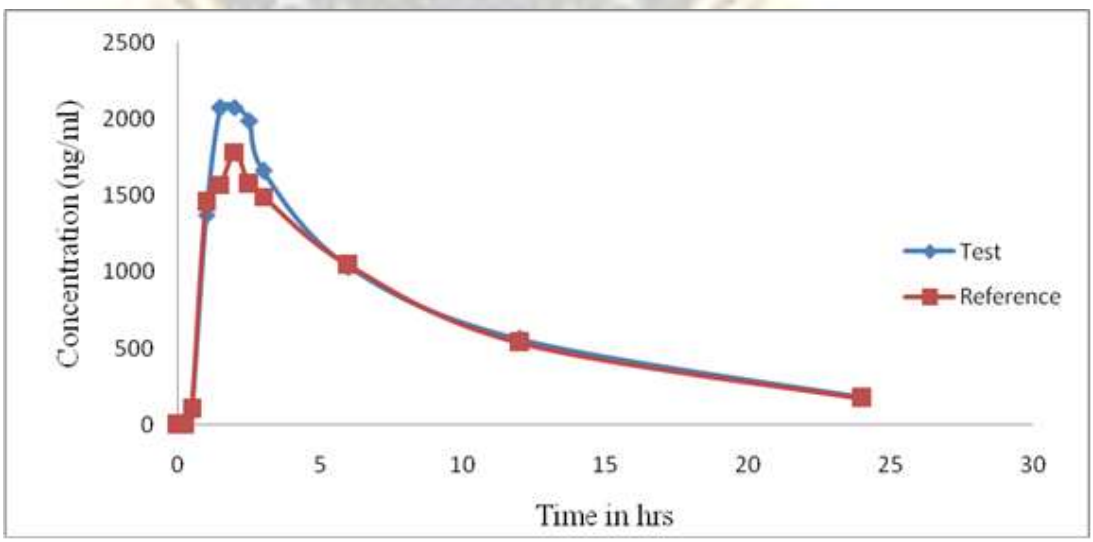

Figure: 5Individual plasma concentrations of test and reference in subject 1003

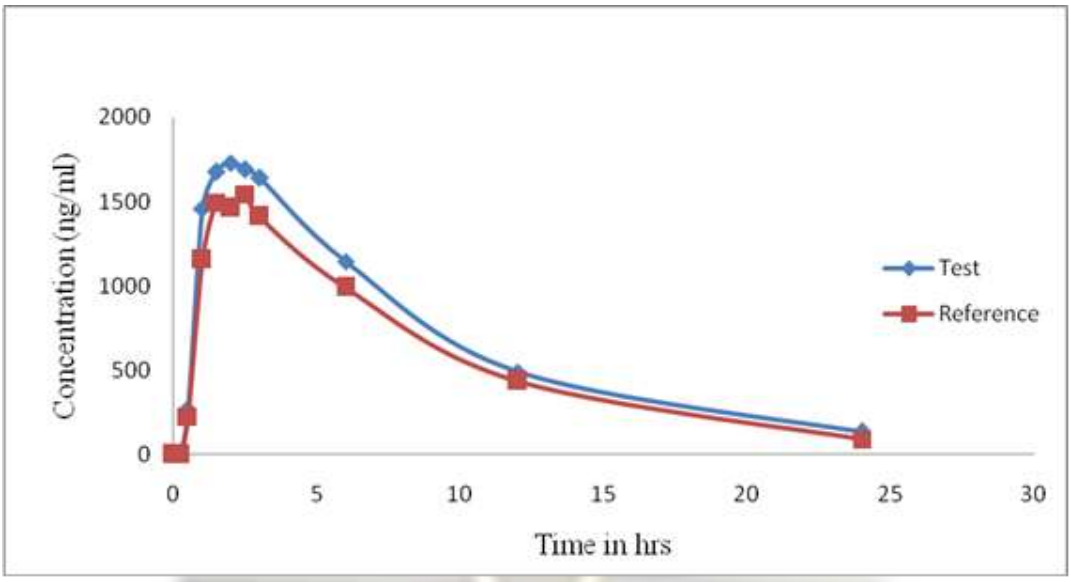

Figure: 6 Individual plasma concentrations of test and reference in subject 1004

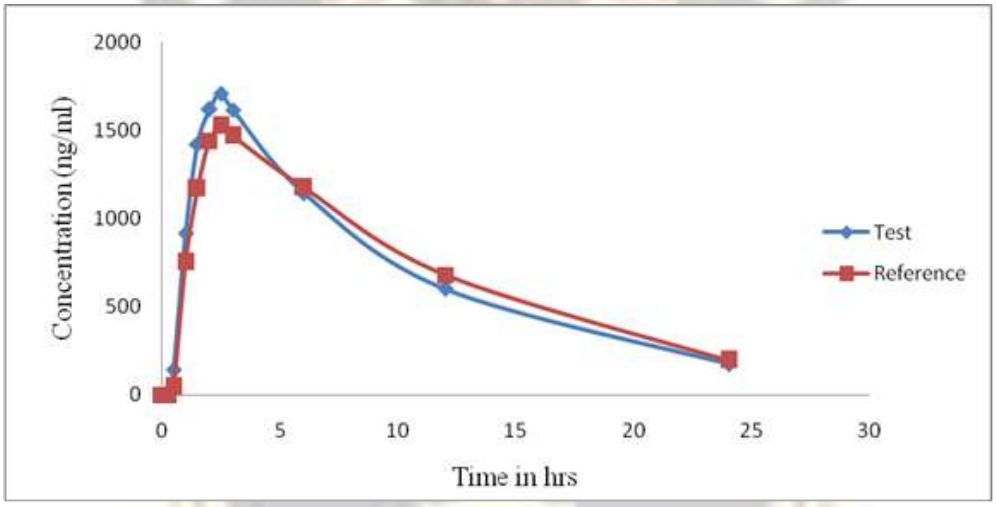

Figure: 7 Individual plasma concentrations of test and reference in subject 1005

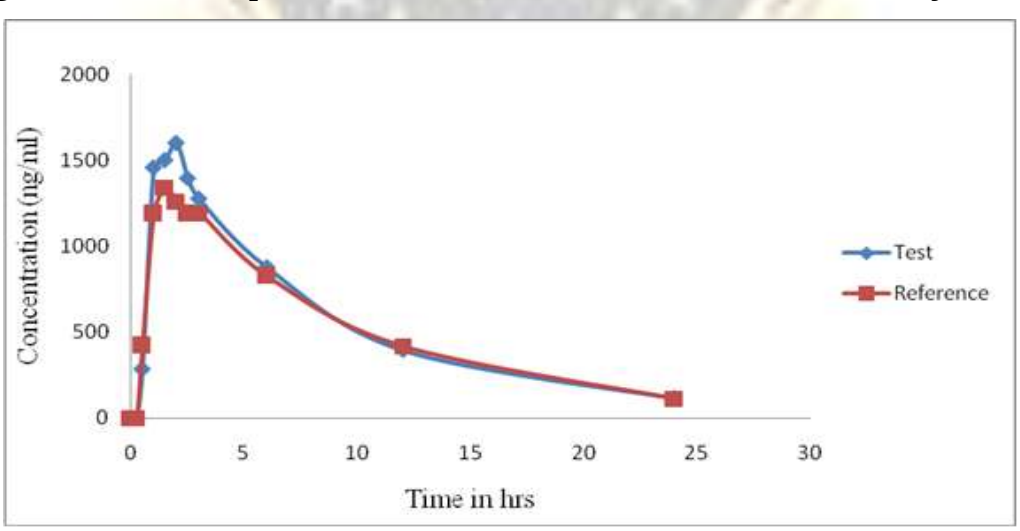

Figure: 8 Individual plasma concentrations of test and reference in subject 1006

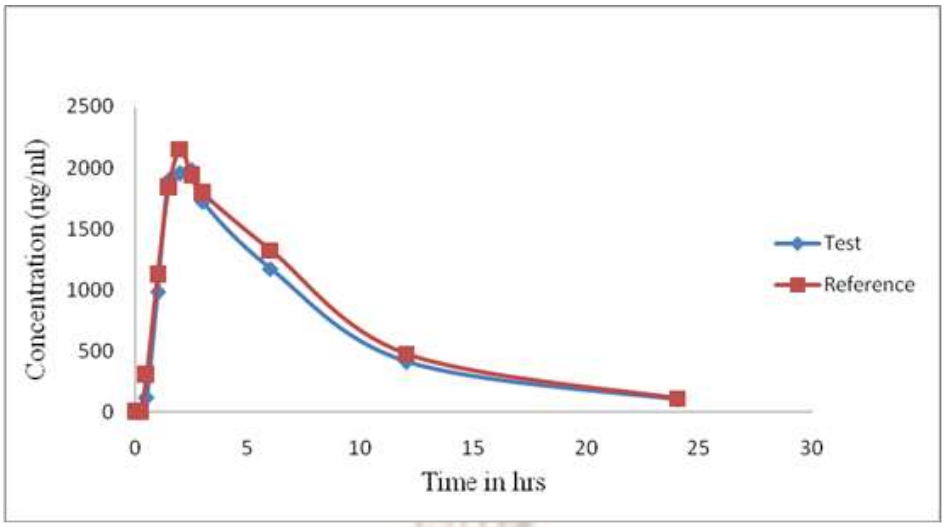

Figure: 9 Individual plasma concentrations of test and reference in subject 1007

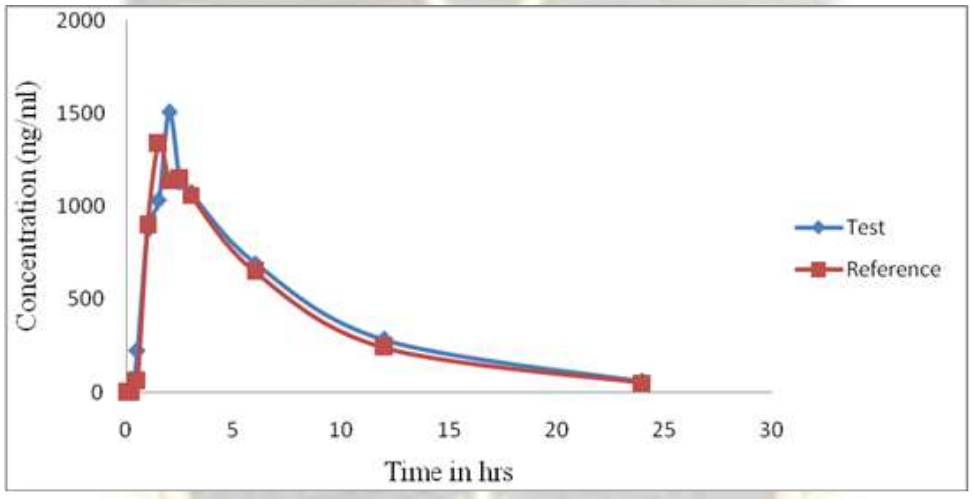

Figure: 10 Individual plasma concentrations of test and reference in subject 1008

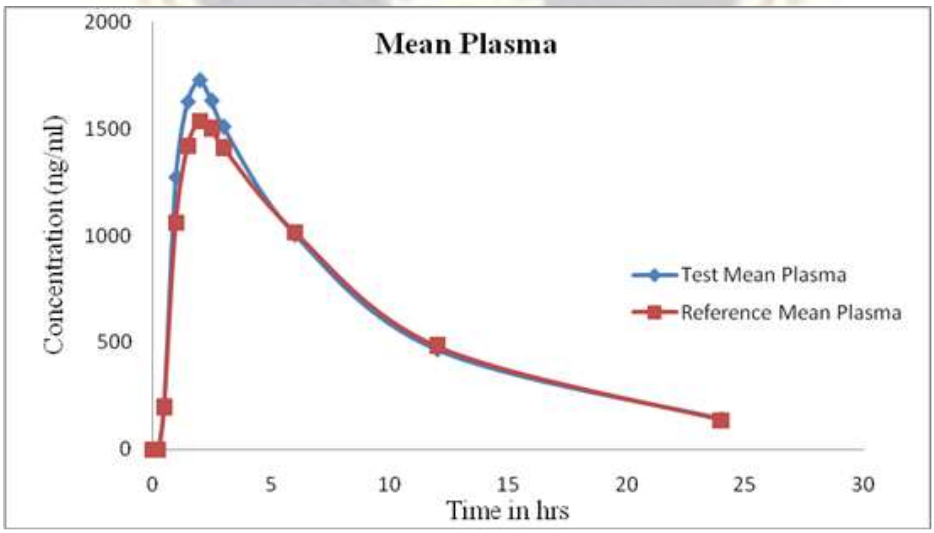

Figure: 11 Comparative mean plasma concentrations of Test Vs Reference of test and reference in subject 1001

Table: 2 Descriptive Statistics of Formulation Means for Nicardipine hydrochloride (n=8)

Parameters (Units)	Mean ± SD (Un – transformed)	
	Test product-T	Reference product
C_{max} (ng/ml)	1725.466 ± 302.54	1536.265 ± 251.65
AUC_{0-t} (ng.h/ml)	1488.098 ± 242.101	1450.378 ± 257.422
$AUC_{0-\infty}$ (ng.h/ml)	1629.404 ± 296.234	1581.535 ± 307.192
AUC_%Extrap_obs (%)	8.287 ± 3.429	7.925 ± 3.373
Tmax (h)	1.844 ± 0.516	2.219 ±0.619
t ½ (h)	1.6 ± 1.272	1.7 ± 1.145

Table: 3 Ratios, 90% Confidence Interval and Power for Nicardipine hydrochloride

Parameters (Units)	Ratio	90% Confidence Interval*		Power
	[A/B]%	Lower	Upper	
C_{max} (ng/ml)	106.76	99.70	114.31	100.00
AUC_{0-t} (ng.h/ml)	102.93	97.31	108.87	100.00
$AUC_{0-\infty}$ (ng.h/ml)	103.27	97.17	109.75	100.00

** 90% Confidence Interval calculated for ln- transformed data*

CONCLUSION

From the above study it was concluded that, the test product Nicardipine Liquid compacts was increases bioavailability with reference product of Nicardipine marketed formulation.

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