Journal Homepage: - www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI: 10.21474/IJAR01/3822
DOI URL: http://dx.doi.org/10.21474/IJAR01/3822
ISSN NO. 2320-5407

RESEARCH ARTICLE

BIOAVAILABILTY STUDY OF NICARDIPINE LIQUISOLID COMPACT TABLETS IN RABBITS AFTER ORAL ADMINISTRATION.

[*]J. Ramesh[1], B. Vijaya kumar[2] and Y. Narasimha Reddy[3].

1. Research Scholar Jawaharlal Nehru Technological University Kakinada, Kakinada, A.P. India.
2. Jangaon Institute Of Pharmaceutical Sciences, Jangaon, Warangal Dist, Telangana, India.
3. University College Of Pharmaceutical Sciences, Warangal Dist, Telangana, India.

Manuscript Info

Manuscript History

Received: 08 February 2017
Final Accepted: 05 March 2017
Published: April 2017

Key words:-
Rabbits, randomised balanced incomplete block design, Wagner nelson method, bio-availability, wash out period.

Abstract

Aim of the present research work is to conduct bio availability study of nicardipine liquisolid compact tablet in rabbit and compare with plain nicardipine drug. Study is conducted by using Randomized Balanced Incomplete Block Design (BIBD) method. Total 8 healthy rabbits were selected with weight of 2.5 kg to 3 kg. Rabbits were labeled by numbers. Each rabbits receiving both formulations after proper wash out period (7 days). Blood samples were collected from marginal ear vein at pre determined time intervals up to 24 Hrs. then blood samples were analyzed by validated high performance liquid chromatography method. Liquisolid compact exhibit c_{max} at 212 ng/ml, t_{max} at 1.63 Hr, $AUC_{(0-t)}$ at 1349 ng.min/ml, $AUC_{(0-\infty)}$ at 1403 ng.min/ml and $t_{1/2}$ at 1.25 hr. AUC and maximum plasma concentration of the liquisolid compact is higher than pure nicardipine drug it indicates liquisolid compacts produce more bioavailability than nicardipine powder.

Introduction:-

Nicardipine is used in the treatment of hypertension (Pompano R et al., 2004; Catarina M et al., 2002). It is calcium channel blocking agent. Nicardipine hydrochloride is a [2-(Benzyl (methyl) amino) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine.3,5-dicarboxylate hydrochloride] (Graham D et al., 1985). Nicardipine have low bio availability due to its low aqueous solubility. So many methods are present to increase solubility of the drug (David et., 2012; Yoshida et al., 2012; Zhang et al., 2012; Sheth et al., 2012). Solubility of nicardipine was increases 10 folds when nicardipine was complexation with carboxylic acid buffer system (Maurin et al., 1994). In the present research work we are using liquid solid compact technique to enhance solubility of nicardipine. To carry out this research work Tween 80 is used as solvent and Avicel and aerosil were used as carrier and as coating material and cross povidone used as super disintegrating agent.

Material and Methods:-

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

Preparation of nicardipine liquisolid compact tablets: 20 mg of nicardipine is solubilised in 200 mg of tween 80. Then to this liquid drug add 512 mg of Avicel as carrier material. Avicel absorb the total liquid drug and turned as

Corresponding Author:- J. Ramesh.
Address:- Research Scholar Jawaharlal Nehru Technological University Kakinada, Kakinada, A.P. India.

wet mass. 52 mg of aerosil is added to the above wet mass and mix it continuously until it produce dried powder. Then 64 mg of cross povidone is added and finally talc and magnesium stearate is added. And mix all the ingredients gently. From this blend we are taken dose according dose calculation for rabbit.

Dose calculation for rabbit:-
Animal dose calculations were based on BSA as per the following formula.
HED (mg/kg) = animal dose (mg/kg) (animal km/human km)
Human equivalent dose (mg/Kg) = 20mg/60kg= 0.33mg/Kg
Km factor for rabbit = 12
Km factor for human = 37
Animal dose (mg/kg) =?
0.33= Animal dose X 12/37
Animal dose= 1.01mg/kg
Animal dose for rabbit weighing 2.5 kg = 2.525 mg of nicardipine

Apparatus and chromatographic condition: 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.

Construction of standard caliberation curve and quality control samples: Stock solutions of nicardipine were prepared by dissolving in methanol (1 mcg/ml). Then again nicardipine solution were diluted with methanol to produce 1, 2, 4, 8, 16, 32, 64 and 128 ng/ml. internal standard solution di ethyl stelbesterol solution further diluted with methanol to produce 1 mg/ml. 1 ml of rabbit plasma is spiked with 25 µL of drug solutions to get 25, 50, 100, 200, 400, 800, 1600 and 3200 ng/ml solutions. In the above concentrated solution 25 µL of internal standard solution was added. From this solution 10µL solution is injected to HPLC. Quality control samples were prepared at concentration 100 ng/ml, 200 ng/ml and 400 ng/ml of nicardipine in blank plasma (Rupender rupali et al., 2014; Leandro tasso et al., 2008)

Administration of the dose and blood sample collection: 8 healthy rabbits were selected with the average weight of 2.5 kg to 3 kg. Two study periods are conducted on each rabbit. Between two study periods one wash out period is maintained i.e., 7 days. Equivalent to 2.5 mg of the nicardipine is taken from liquisolid compact powder and it is dispersed in 0.25% carboxy methyl cellulose. Then drug solution administered through oral feeding tube (Nanda gopal anitha et al., 2014). Then at predetermined time intervals blood samples were collected up to 24 hrs from marginal ear vein at 0.0, 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 6.00, 12.00 and 24.00 Hrs. blood samples were collected in heparin contain test tubes. Then separation of plasma done by centrifugation process at 5000 rpm for 5min and stored under frozen condition till the analysis was performed.

Sample preparation: 0.5 ml plasma sample is transferred to 2 ml of test tube then 10 mcg/ml of di ethyl stelbesterol was added and centrifuged then supernatant was removed. 200 µL of methanol was added and mix well then centrifuge for 5 min for separation of phases then evaporate at room temperature. Then again 200 µL of mobile phase was added then 10µL solution is injected to HPLC.

Method validation: linearity was determined (Meiling et al. 2006) by preparing 3 sets of samples at the concentration of 25, 50, 100, 200, 400, 800, 1600 and 3200 ng/ml. inter day precission was evaluated on 100 ng/ml, 200 ng/ml and 400 ng/ml samples on 3 different days. Intraday precission (Ashesh bhandary et al., 2013) was evaluated on five sets of 100 ng/ml 200ng/ml and 400 ng/ml samples on the same day. QC recovery was conducted on three set on 100 ng/ml, 200 ng/ml and 400 ng/ml.

Data analysis: Pharmaco kinetic parameters were calculated by Wagner nelson method. C_{max}, T_{max}, $t_{1/2}$, k_{el}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ were evaluated in individual rabbit.

Result and discussion:-

Linearity: linearity was determined on 3 sets of samples concentration of 25 ng/ml, 50 ng/ml, 100 ng/ml, 200 ng/ml, 400 ng/ml, 800 ng/ml, 1600 ng/ml and 3200 ng/ml were used to draw caliberation curve. Caliberation curve give linear regression equation y = 0.009x-0.144 and the correlation co efficient value r^2 was 0.999 (Figure 1)

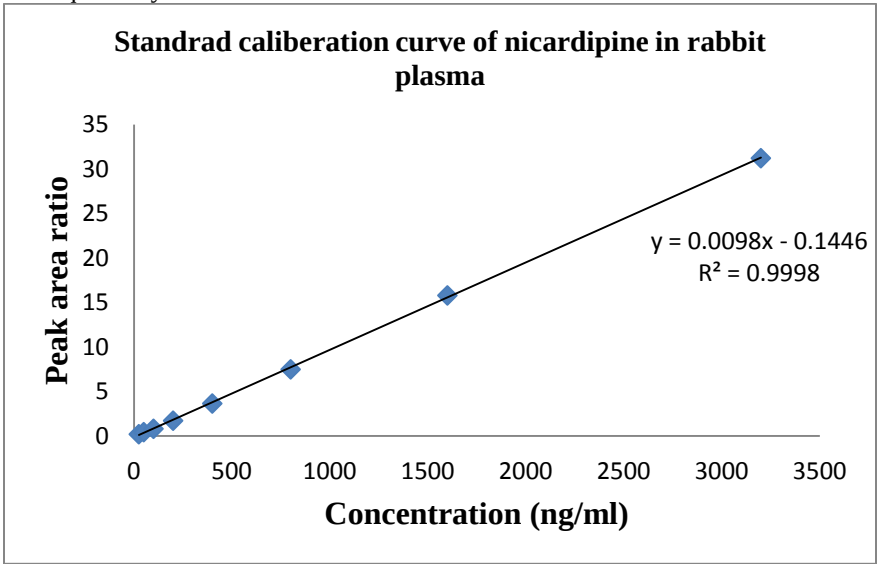

Figure 1:- linear caliberation curve of nicardipine in rabbit plasma

Precission: the inter day and intraday precission were expressed in % relative standard deviation (Onkar jagtap wt al., 2011). Relative standard deviation for inter day precission were from 0.1 to 0.21 (table no 1) and intraday precission were from 0.11 to 0.22 (table no 2). All the RSD values less than 2 it indicted values are within the acceptable limit.

Table no 1:- Inter day precission

Concentration (ng/ml)	Inter day precision		
	100 ng/ml	200 ng/ml	400 ng/ml
Day 1	20779	41095	102334
Day 2	20861	41124	102125
Day 3	20790	41281	102241
Mean	20810	41166	102233
SD	44.51	100.07	104.71
% Rsd	0.21	0.24	0.10

Table no 2:- Intraday precission:

Concentration (ng/ml)	Intraday precision data		
	100 ng/ml	200 ng/ml	400 ng/ml
Area 1	20850	41058	102124
Area 2	20905	41085	102284
Area 3	20875	41125	102115
Area 4	20921	41278	102294
Area 5	20890	41064	102354
Mean	20888.2	41122	102234.2
SD	27.36	91.07	108.12
% Rsd	0.13	0.22	0.11

QC recovery: recovery of qc sample were from 99 to 105% (table. 3)

Table no 3:- QC recovery

Concentration (ng/ml)	% Recovery
100	99
200	105
400	102

Pharmacokinetic of nicardipine:-

The individual plasma concentrations of test and reference products in each subject were given in Table 4 and 5. Individual pharmacokinetics parameters of test and reference product in each subject was given in table 6 and 7 .The plots of comparative mean plasma concentrations of test and reference products in Rabbit were shown in figure 2.

The mean peak plasma concentration of test (T) formulation C_{max} 212.25 ng/ml was gradually reached in 1.63 hr. In case of conventional reference formulation (R) the C_{max} was 125.25ng/ml. It takes time 1.8 hr. The C_{max} of the Test formulation (T) was higher when compared with Reference (R) formulation. The lower in T_{max} of test formulation (1.63) was clearly indicating the drug shown quicker on set action when compared to reference product. The AUC_{0-t} of the reference (R) was found to be 1017.65ng.min/ml. The increase in AUC_{0-t} was observed in the test (T) formulation, which was around 1348.95ng.min/ml. This clearly indicates the drug shown higher bio-availability than reference formulation.

Decrease in elimination rate constant (K_{el}) from 0.59 hr-1 (Test) to 0.23 hr-1 (reference) indicates the reference formulation shown slow release rate of the drug in the body. Test formulation fastly releases the drug in the body. Half life of test product (1.25 hr) is lower compare to reference product (3.06 hr) it indicates test product fastly absorbed and shows faster action.

Table no 4:- Individual concentrations of Nicardipine after administration of Test product in each subject

		Plasma concentration (ng) of optimized nicardipine liquisolid compact tablet (Test)										
Subject	Study period	Time in Hrs										
		0	0.25	0.5	1	1.5	2	2.5	3	6	12	24
1001	1	0	30	60	115	170	227	190	85	64	45	34
1002	2	0	80	110	152	210	171	121	72	57	49	27
1003	1	0	60	86	145	162	195	114	98	65	41	37
1004	2	0	74	104	161	227	137	111	99	67	33	21
1005	1	0	54	69	148	178	139	114	91	66	37	29
1006	1	0	57	76	137	219	164	130	78	61	42	33
1007	1	0	65	115	159	221	147	114	68	51	42	31
1008	2	0	71	95	161	221	135	112	72	61	44	34
N		8	8	8	8	8	8	8	8	8	8	8
Mean		0	61.38	89.38	147.25	201.00	164.38	125.75	82.88	61.50	41.63	30.75
SD		0	15.45	19.99	15.54	26.44	32.65	26.70	12.19	5.35	4.90	5.04
Min		0	30	60	115	162	135	111	68	51	33	21
Median		0	62.5	90.5	150	214.5	155.5	114	81.5	62.5	42	32
Max		0	80	115	161	227	227	190	99	67	49	37

Table no 5:- Individual concentrations of Nicardipine after administration of Reference product in each subject

		Plasma concentration (ng) of nicardipine conventional tablet (Reference)										
Subject	Study period	Time in Hrs										
		0	0.25	0.5	1	1.5	2	2.5	3	6	12	24
1001	2	0	21	41	85	112	124	94	84	54	37	21
1002	1	0	15	35	75	111	118	105	74	55	37	22
1003	2	0	18	31	71	117	121	105	94	47	31	19
1004	1	0	16	29	84	114	131	117	91	41	27	20
1005	2	0	18	36	91	128	116	102	87	52	34	18
1006	1	0	11	39	82	117	127	112	89	47	31	23
1007	2	0	27	48	79	119	109	98	83	45	29	19
1008	1	0	22	37	89	109	137	121	93	48	32	24
N		8	8	8	8	8	8	8	8	8	8	8
Mean		0	18.5	37	82	115.87	122.87	106.75	86.87	48.62	32.25	20.75
SD		0	4.86	5.92	6.78	5.96	8.87	9.28	6.53	4.74	3.57	2.12
Min		0	11	29	71	109	109	94	74	41	27	18
Median		0	18	36.5	83	115.5	122.5	105	88	47.5	31.5	20.5
Max		0	27	48	91	128	137	121	94	55	37	24

Table 7:- Pharmaco kinetic data of Test product-T in each subject

Pharmacokinetic data of optimized nicardipine liquisolid compact tablets (Test)							
Treatment	Subject	T_{max}	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	K_{el}	$t_{1/2}$
Test	1	2	227	1426.75	1461.35	0.98	0.7
	2	1.5	210	1373.75	1412.77	0.69	1
	3	2	195	1410.25	1464.01	0.68	1
	4	1.5	227	1273.25	1323.13	0.42	1.64
	5	1.5	178	1292.12	1350.74	0.49	1.4
	6	1.5	219	1354.75	1425.75	0.46	1.49
	7	1.5	221	1292.37	1353.33	0.5	1.36
	8	1.5	221	1368.37	1436	0.5	1.37
N		8	8	8	8	8	8
Mean		1.63	212.25	1348.95	1403.39	0.59	1.25
SD		0.23	17.36	57.32	53.99	0.19	0.31

Table 8:- Pharmaco kinetic data of Reference product-R in each subject

Pharmacokinetic data of conventional nicardipine tablets (Reference)							
Treatment	Subject	$T_{max\ (hr)}$	$C_{max\ (ng/ml)}$	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	K_{el}	$t_{1/2}$
Reference	1	2	124	1077.12	1170.46	0.22	3.08
	2	2	118	1063.37	1157.59	0.23	2.96
	3	2	121	992.12	1059.09	0.28	2.44
	4	2	131	944.62	1033.08	0.22	3.06
	5	1.5	128	1036.75	1128.16	0.19	3.51
	6	2	127	1020.62	1112.1	0.25	2.75
	7	1.5	119	950	1039.28	0.21	3.25
	8	2	134	1056.62	1174.19	0.2	3.39
N		8	8	8	8	8	8
Mean		1.88	125.25	1017.65	1109.24	0.23	3.06
SD		0.23	5.75	50.82	58.41	0.03	0.35

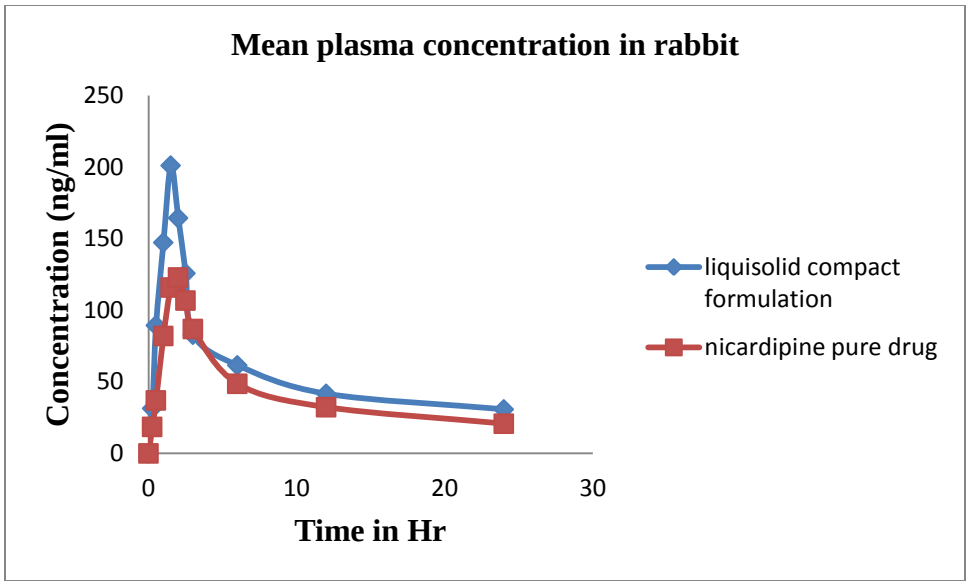

Figure 2:- mean plasma concentration of test and reference formulation

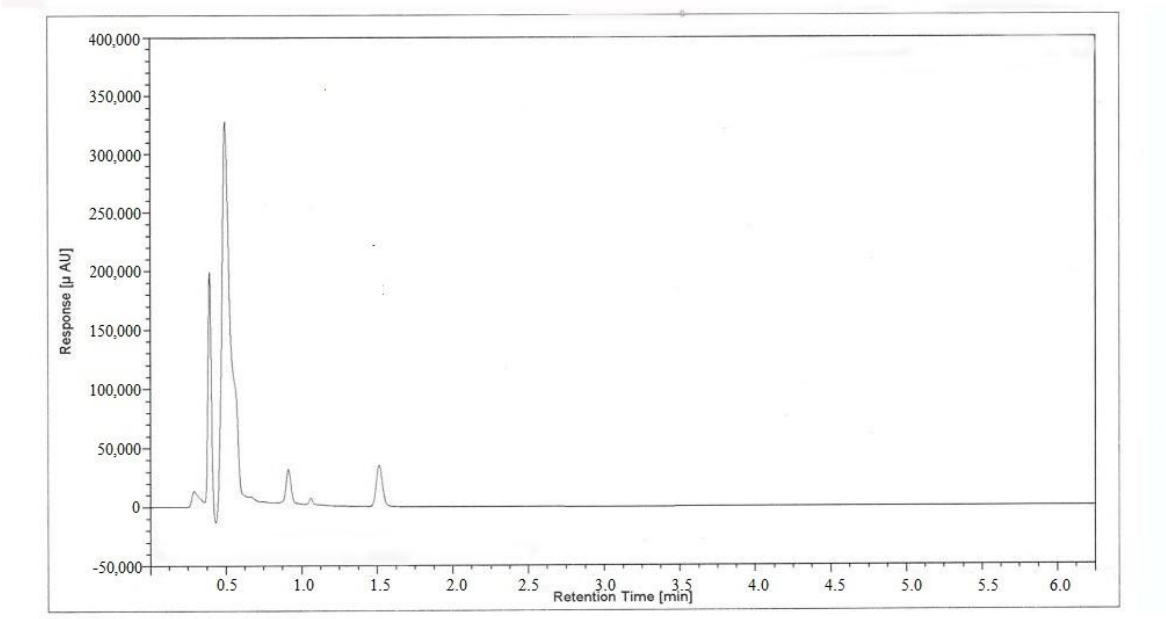

Figure 3:- HPLC spectra of blank rabbit serum

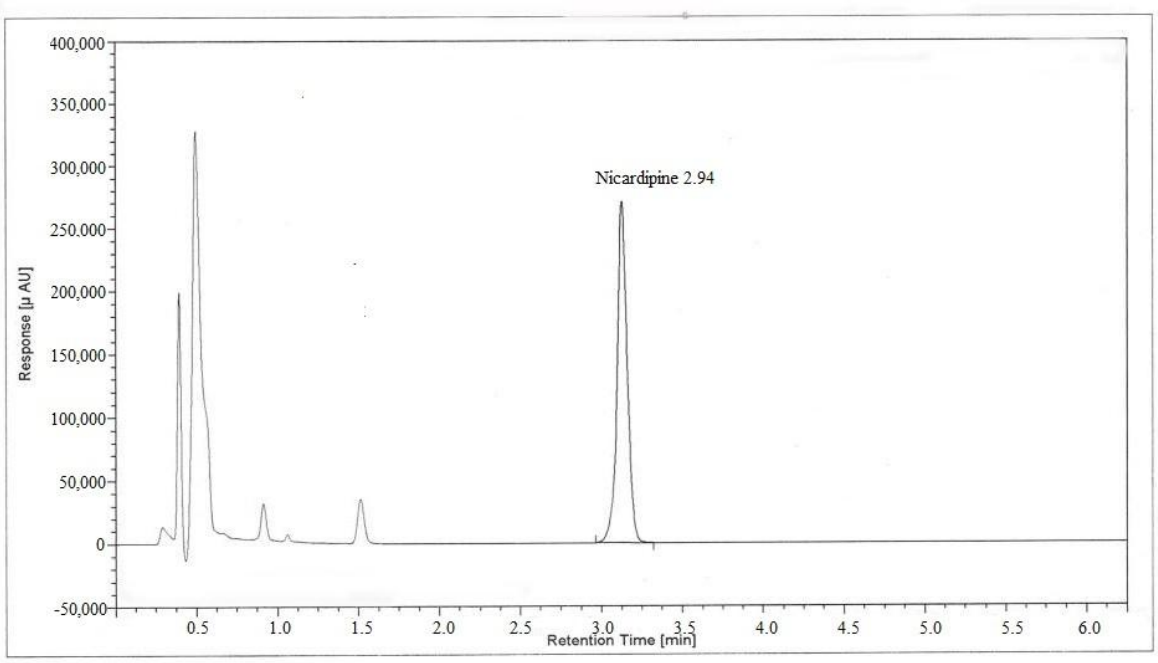

Figure 4:- HPLC spectra of nicardipine

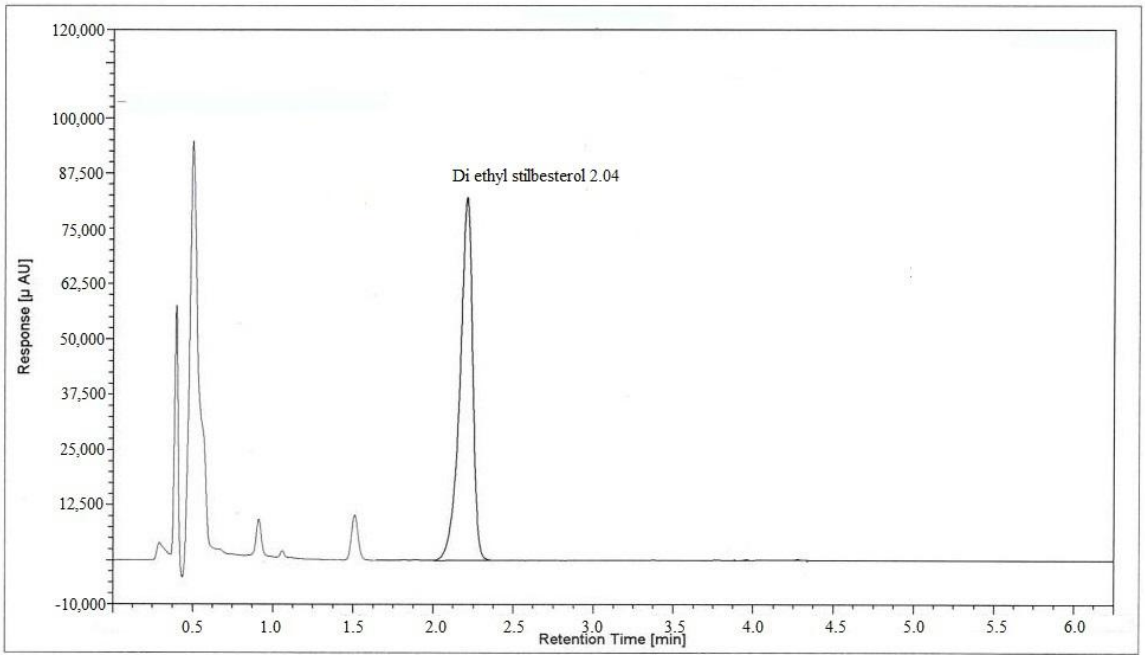

Figure 5:- HPLC spectra of Di ethyl stelbesterol

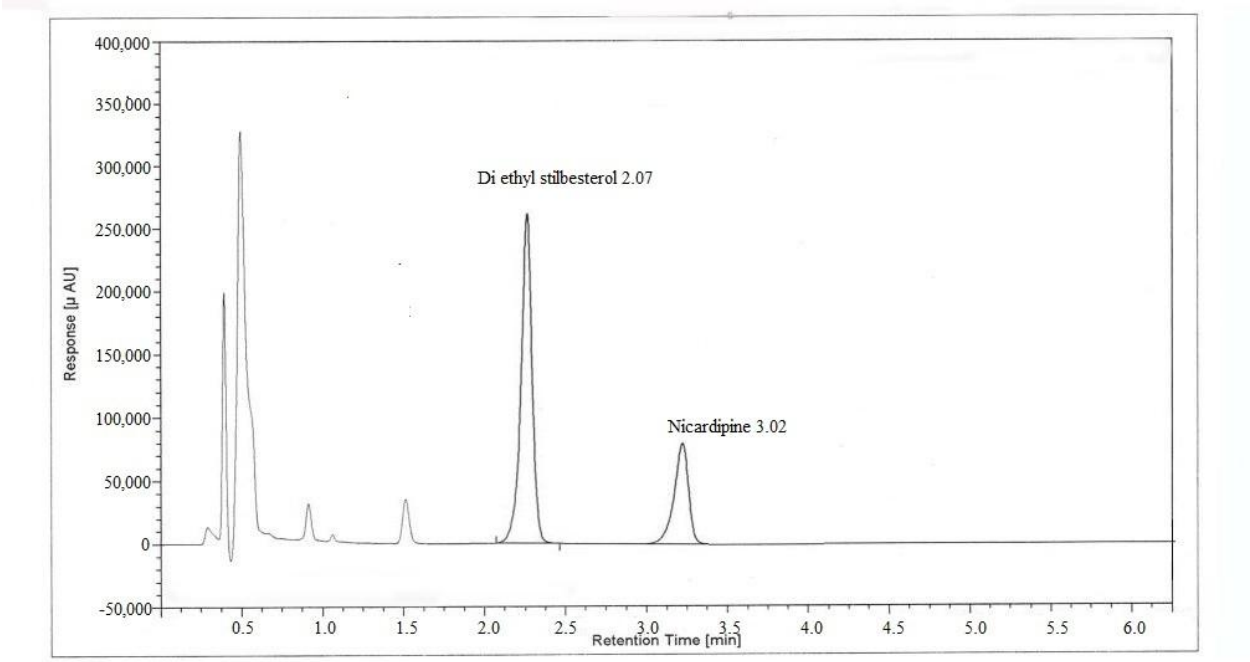

Figure 6:- HPLC spectra of nicardipine and di ethyl stilbesterol

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.

References:-

1. Ashesh Bhandary, Arpana Pradhan Bhandary, Gulam Muhammad Khan and Bijay aryal (2013): Non-Compartmental Pharmacokinetics Modeling Of Amlodipine In Rats: Int. Res J Pharm. App Sci., 3(5):120-126.
2. Catarina M, Fernandes J and Veiga B (2002): Physicochemical characterization and in vitro dissolution behavior of nicardipine cyclodextrins inclusion compounds: Eur J Pharm Sci., 15(1):79–88.
3. David SE, Timmins P, Conway BR (2012): Impact of the counter ion on the solubility and physicochemical properties of salts of carboxylic acid drugs: Drug Dev Ind Pharm., 38(1): 93-103.
4. Graham D.J.M, Dow R.J, Freedman D, Hall DJ, Alexander OF and Mroszczak EJ (1985): The metabolism and pharmacokinetics of nicardipine hydrochloride in man: Br.J.Clin.pharmacol., 20(1): 233-285.
5. Leandro tasso , Clarissa C. Bettoni and Teresa dalla costa (2008): Pharmacokinetic Plasma Profile and Bioavailability Evaluation of Gatifloxacin in Rats: Latin American Journal of Pharmacy., 27(2): 270-273.
6. Maurin MB, Rowe SM, Koval CA and Hussain MA (1994): Solubilization of nicardipine hydrochloride via complexation and salt formation: J Pharm Sci.,83(10):1418-1420.
7. Meiling Q, Peng W and Xin J (2006): Liquid chromatography–mass spectrometry method for the determination of nicardipine in human plasma: J Chromatogr B analyt technol biomed life sci., 830(1): 81–85.
8. Nanda Gopal Anitha , Kalyan Chandra Gurajapu and Tirunagari Mamatha (2014): Study Of Pharmacokinetic And Pharmacodynamic Drug – Drug Interaction Between Rosuvastatin And Glimepiride In Normal Rabbits: world journal of pharmacy and pharmaceutical sciences.,4(1):1218-1230.
9. Onkar Jagtap, Vijaya Godse, Sangeeta deshpande and Meenakshi deodhar (2011): HPLC Determination of Satranidazole in Rat Plasma: Asian Journal of Chemistry., 23(10): 4317-4320.
10. Pomponio R, Gotti R and Fiori J (2004): Photostability studies on nicardipine cyclodextrin complexes by capillary electrophoresis: J Pharm and Biomed Anal., 35(2):267–275.
11. Rupender Rupali, Karambir Singh Dhot, KB Ilango and Shaik shabbier (2012): Pharmacokinetic Studies Of Ambroxol Hydrochloride Microspheres In Rats After Oral Administration: International Journal Of Research In Pharmacy And Chemistry., 2(2):280-288.

12. Sheth P, Sandhu H, Singhal D, Malick W, Shah N and Kislalioglu MS (2012): Nanoparticles in the pharmaceutical industry and the use of supercritical fluid technologies for nanoparticle production: Curr Drug Deliv., 9(3): 269-284.
13. Yoshida T, Kurimoto I, Yoshihara K, Umejima H, Ito N, Watanabe S, Sako K and Kikuchi A (2012): Aminoalkyl methacrylate copolymers for improving the solubility of tacrolimus-I Evaluation of solid dispersion formulations: Int J Pharm., 428(1): 18–24.
14. Zhang Y, Wang J, Bai X, Jianq T, Zhang Q and Wang s (2012): Mesoporous silica nanoparticles for increasing the oral bioavailability and permeation of poorly water soluble drugs: Mol Pharm., 9(3): 505-513.