IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
January 2021 Vol.:20, Issue:2

Bioequivalence study of test formulations T1 and T2 Nadolol tablets USP with reference formulation in healthy adult, human subjects under fed conditions

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Shubham A. Garibe[1], Ravindra L. Bakal[1,*], Jagdish V. Manwar[2], Nitin I. Kochar[3]

1 Dr. Rajendra Gode Institute of Pharmacy, Mardi Road, Amravati-444 602, MS, India, 2 Dr. Rajendra Gode College of Pharmacy, Mardi Road, Amravati-444 602, MS, India, 3 P. Wadhwani College of Pharmacy, Yavatmal-445 001, MS, India.

Submitted: 05 December 2020
Revised: 26 December 2020
Accepted: 16 January 2021

Keywords: Nadolol, Bioequivalence, Pharmacokinetic, Fed condition

ABSTRACT

A randomized, open label, balanced, three-treatment, three-sequence, three-period, single dose, three-way crossover, oral bioequivalence assay in healthy adult, human subjects, under fed conditions determined from blood plasma sample collected. The test formulations T1 and T2 Nadolol Tablets USP 80 Mg with reference formulation Nadolol Tablets USP 80 mg. A total of 18 healthy human adult male subjects were recruited for the study. The final pharmacokinetic and statistical analysis was performed with all 15 subjects. Study concluded that test products Nadolol tablets concluded to not bio-equivalent to the reference product.

HUMAN JOURNALS
www.ijppr.humanjournals.com

INTRODUCTION

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent of absorption) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy. Bioequivalence studies are a surrogate marker for clinical effectiveness and safety data as it would not normally be practical to repeat clinical studies for generic products. It is accepted that if plasma concentrations of the active ingredient of the generic and innovator medicines are the same, then their concentration at the site of action and therefore their safety and effectiveness will be the same.

Nadolol **(Figure No. 1)** is a synthetic non-selective beta-adrenergic receptor blocking agent designated chemically as 1-(tert-butylamino)-3-[(5, 6, 7, 8-tetrahydro-cis-6, 7-dihydroxy-1-naphthyl) oxy]-2-propanol. Nadolol is a white crystalline powder. It is freely soluble in ethanol, soluble in hydrochloric acid, slightly soluble in water and in chloroform, and very slightly soluble in sodium hydroxide.

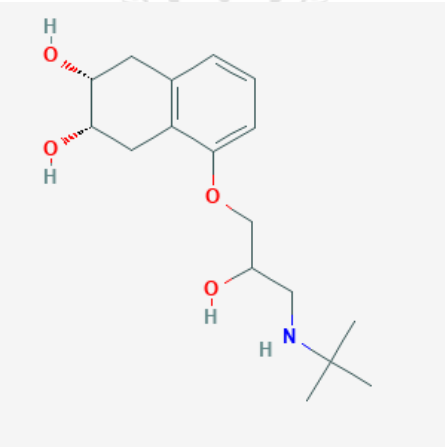

Figure No. 1: Structural Formula of Nadolol

Non-selective β-adrenergic blocking agent (β-blocker): Nadolol competes with adrenergic neurotransmitter such as catecholamine for binding at sympathetic receptor sites, in the heart and vascular smooth muscle, inhibiting the effect of catecholamine epinephrine and norepinephrine and decreasing heart rate, cardiac output, systolic and diastolic blood pressure. It also blocks beta-2 adrenergic receptors located in bronchiole smooth muscle causing bronchoconstriction. By binding juxtaglomerular apparatus, Nadolol inhibit the production of renin thereby inhibiting the angiotensin II and aldosterone production. Nadolol

thus inhibits vasoconstriction and water retention due to angiotensin II and aldosterone respectively.

MATERIALS AND METHODS

Study design: open label, randomized, balanced, three-treatment, three-sequence, three period, single dose, three-way crossover, and oral bioequivalence study under fed condition. Volunteer screening record (VSR) file: The following documents were used during the screening and recruitment of volunteers: screening consent form; demographics, general physical and systemic examination forms; ECG; chest X-ray reports; HIV counselling & test record and inclusion and exclusion criteria.

Consent obtained from 18 volunteers and all these subjects were admitted as per the admission procedures detailed in this protocol.

A balanced block randomization schedule was generated before the start of study by using SAS®software version 9.2 (or higher version available). According to the randomization schedule, subjects has received the assigned formulation in each period, with the possible sequences,, T1T2R‟ (where T1= Test Formulation-1, T2 = Test Formulation-2 and R = Reference Formulation).

Admission Day: The principal investigator has informed the subjects before initiation of study through an oral presentation of informed consent document regarding the purpose, procedures to be carried out, potential risks and benefits and rights of the subjects. Sitting posture vital sign's like BP (blood pressure), PR (pulse rate), RR (respiratory rate), & oral body temperature.

Medical examination: physical and systemic examination Medication history recording. Urine test for drug(s) of abuse (amphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine and morphine) Breath test for alcohol consumption.

Sampling Schedule: A total of 25 blood samples were collected during the study from each subject. 1 pre-dose blood sample of 6mL and 24 post-dose blood samples of 4 mL each had drawn at 1.00, 1.50, 2.00, 2.25, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 4.75, 5.00, 5.50, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 and 72.00 hours after the actual start time of the drug administration under normal light condition.

Sample Collection, Processing and Transfer Procedures: Blood samples were collected through an indwelling cannula placed in a forearm vein using vacutainers and Luer adaptor or through fresh vein puncture in case of cannula blockage. Heparin-lock technique (about 0.5 mL of 05 IU/ mL heparin in normal saline solution had injected into the cannula after each sample collection) had used to prevent clotting of the blood in the indwelling cannula. Twenty-five (25) blood samples were withdrawn after discarding 0.5 mL of heparinised blood each time (except for the samples collected through fresh prick) at each sampling time point.

RESULTS AND DISCUSSION

Pharmacokinetic parameters: The primary parameters were Cmax, AUC0-t and AUC0-inf which underwent descriptive and comparative statistical evaluation. And the secondary parameters were Tmax, T1/2el, Kel, AUC_% Extrap, TLIN and LQCT which underwent descriptive statistical evaluation. The following pharmacokinetic parameters were estimated by using Phoenix ® WinNonlin®.

Subject's Demographic Profile: Subject's demographic profile consist of all 18 male subjects of Age in between 18-43 (in years), Height 156.5-179.8 (In Cm), and Weight in range of 51-73 (In Kg).

Randomization schedule: A balanced block randomization schedule was generated before the start of study by using SAS® software version 9.4, SAS Enterprise Guide 6.1. According to the randomization schedule (**Table No. 1**), subjects were administered the assigned formulation in each period, with the following sequences 'T1T2R' or 'T2RT1' or T2T1R.

Table No. 1: Randomisation schedule

Sr. No.	Sequence	Period I	Period II	Period III
1	T1T2R	Test Formulation - T1	Test Formulation - T2	Reference - R
2	T2T1R	Test Formulation - T2	Test Formulation - T1	Reference - R
3	RT1T2	Reference – R	Test Formulation - T1	Test Formulation - T2
4	T2RT1	Test Formulation - T2	Reference – R	Test Formulation - T1
5	T1T2R	Test Formulation - T1	Test Formulation - T2	Reference - R
6	RT1T2	Reference – R	Test Formulation - T1	Test Formulation - T2
7	T2RT1	Test Formulation - T2	Reference – R	Test Formulation - T1
8	RT1T2	Reference – R	Test Formulation - T1	Test Formulation - T2
9	T1T2R	Test Formulation - T1	Test Formulation - T2	Reference - R
10	RT1T2	Reference – R	Test Formulation - T1	Test Formulation - T2
11	T1T2R	Test Formulation - T1	Test Formulation - T2	Reference – R
12	T2RT1	Test Formulation - T2	Reference – R	Test Formulation - T1
13	T1T2R	Test Formulation - T1	Test Formulation - T2	Reference – R
14	T2RT1	Test Formulation - T2	Reference – R	Test Formulation - T1
15	RT1T2	Reference – R	Test Formulation - T1	Test Formulation - T2
16	RT1T2	Reference – R	Test Formulation - T1	Test Formulation - T2
17	T1T2R	Test Formulation - T1	Test Formulation - T2	Reference - R
18	T2RT1	Test Formulation - T2	Reference – R	Test Formulation - T1

(Where, T1= Test Formulation One, T2= Test Formulation Two, and R = Reference Formulation). Equal allocation of subjects to each sequence was ensured).

Graphical Representation: An average plasma concentration vs. time curve of test and reference Nadolol tablets are almost same and figure no. 2 and 3 shows that average plasma concentrations Vs. time curve of test and reference Nadolol tablets (semi log) are almost same **(Table No. 2 & 3)**.

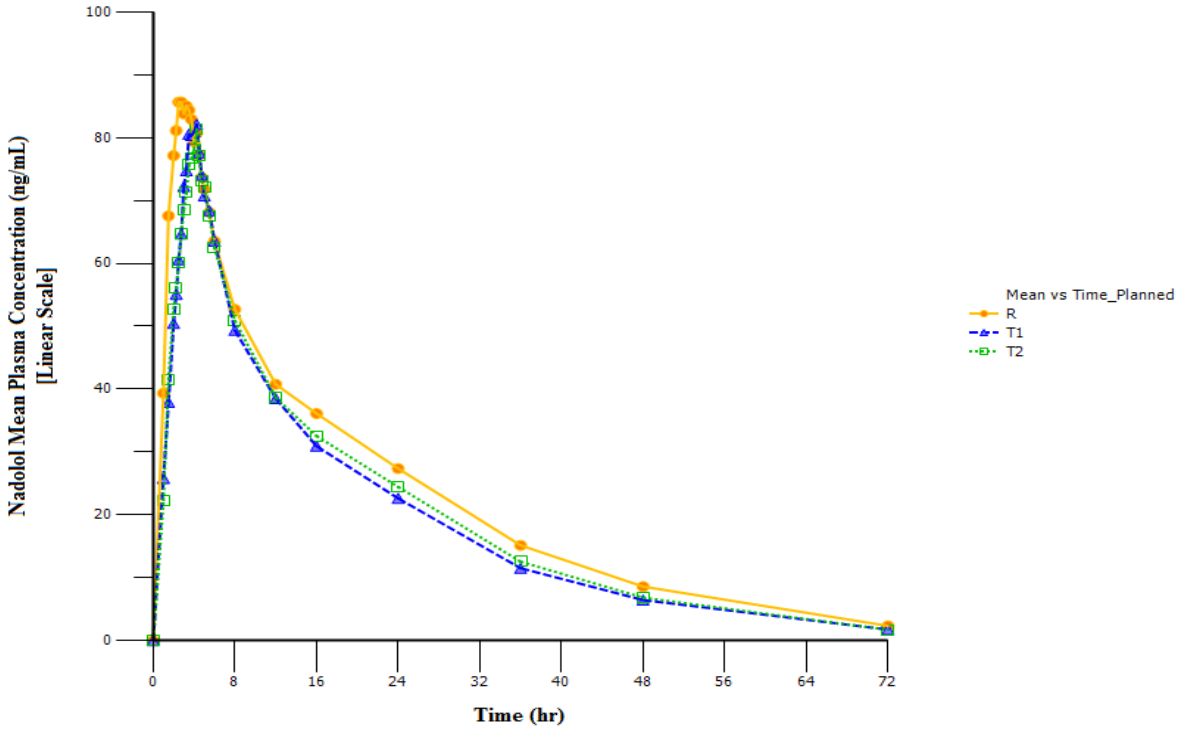

Figure No. 2: Average plasma concentrations Vs. time curve of test and reference Nadolol tablets (Linear Scale)

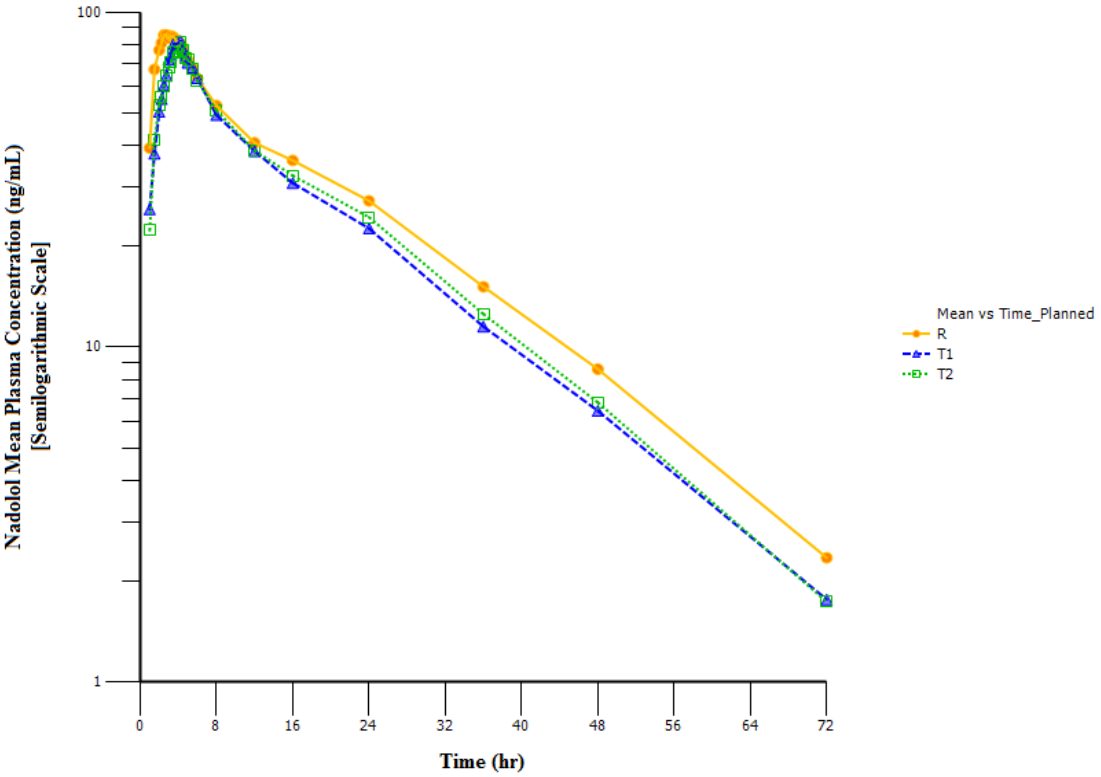

Figure No. 3: Average plasma concentrations Vs. time curve of test and reference Nadolol tablets (Semi log arithmetic Scale)

Table No. 2: Analysis of Variance (ANOVA) Results

Untransformed Data			
TEST (T1)			
Arithmetic Mean	91.0772	1381.2872	1428.3023
S.D.	26.46005	407.51120	419.04539
C.V.(%)	29.05	29.50	29.34
N	15	15	15
TEST (T2)			
Arithmetic Mean	93.4599	1421.0600	1470.7814
S.D.	30.69485	382.39445	397.99920
C.V.(%)	32.84	26.91	27.06
N	15	15	15
REFERENCE (R)			
Arithmetic Mean	100.9263	1622.6399	1686.6740
S.D.	36.88954	497.85510	517.33591
C.V.(%)	36.55	30.68	30.67
N	15	15	15

Cmax, AUC0-t and AUC0-inf of Test-1, Test-2 and Reference product.

Table No. 3: Analysis of variance (ANOVA) Result

	Cmax [ng/mL]	**AUC0-t [ng*hr/mL]**	**AUC0-inf [ng*hr/mL]**
Geometric Mean(T1)	87.2657	1312.8507	1359.1662
Geometric Mean(T2)	88.7998	1361.5021	1409.5405
Geometric Mean(R)	95.7373	1552.5073	1611.5201
T1/R Ratio(%)	91.15	84.56	84.34
90% C.I. (T1 vs. R)	81.72 — 101.67	78.19 — 91.46	77.79 — 91.44
T2/R Ratio(%)	92.75	87.70	87.47
90% C.I. (T2 vs. R)	83.15 — 103.46	81.09 — 94.85	80.67 — 94.83
Inter subject C.V.(%)	36.37	30.75	30.29
Intra subject C.V.(%)	17.56	12.55	12.95
Power(%)	95.64	99.80	99.71

CONCLUSION

The 90% confidence interval of the ratio of geometric means for the test-1 and reference formulations for Cmax was found to be 81.72% to 101.67%, which is within the acceptance interval of 80.00% to 125.00%. The 90% confidence interval of the ratio of geometric means for the test-1 and reference formulations for AUC0-t was found to be 78.19% to 91.46%, which is not within the acceptance interval of 80.00% to 125.00%. The 90% confidence interval of the ratio of geometric means for the test-1 and reference formulations for AUC0-inf was found to be 77.79% to 91.44%, which is not within the acceptance interval of 80.00% to 125.00%.

The 90% confidence interval of the ratio of geometric means for the test-2 and reference formulations for Cmax was found to be 83.15% to 103.46%, which is within the acceptance interval of 80.00% to 125.00%. The 90% confidence interval of the ratio of geometric means for the test-2 and reference formulations for AUC0-t was found to be 81.09% to 94.85%, which is within the acceptance interval of 80.00% to 125.00%. The 90% confidence interval of the ratio of geometric means for the test-2 and reference formulations for AUC0-inf was found to be 80.67% to 94.83%, which is within the acceptance interval of 80.00% to 125.00%.

The products (T1, T2) Nadolol tablets concluded to not bio-equivalent to the reference product in Healthy Adult, Human Subjects.

REFERENCES

1. Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI, 2005, Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI.
2. Accesson:29/Nov/2017 https//www.accessdata.fda.gov/drugsatfda_docs/label/2008/018063s060lbl.html For relevant pharmacokinetic parameter reference: Prescribing information of CORGARD® (Nadolol) Tablets, text revised on JUL 2013.
3. Misaka S, Miyazaki N, Yatabe MS, Ono T, Shikama Y, Fukushima T, Kimura J. (2013) Pharmacokinetic and pharmacodynamic interaction of Nadolol with itraconazole, rifampicin and grapefruit juice in healthy volunteers. The Journal of Clinical Pharmacology. 1;53(7):738-45.
4. Mehta AV, Chidambaram B. (1992) Efficacy and safety of intravenous and oral Nadolol for supraventricular tachycardia in children. Journal of the American College of Cardiology. 19(3):630-5.
5. Khuri SF, Okike ON, Josa M, Vander Salm TJ, Assoussa S, Leone L, Silverman A, Siouffi S, Olukotun AY. (1987) Efficacies of Nadolol in preventing supraventricular tachycardia after coronary artery bypass grafting. The American journal of cardiology:60(6):51-8.
6. Wallin JD, Shah SV. (1987) ß-Adrenergic Blocking Agents in the Treatment of Hypertension: Choices Based on Pharmacological Properties and Patient Characteristics. Archives of internal medicine. 147(4):654-9.
7. CDSCO Ministry of health and family welfare, Government of India, New Delhi, March 2005.
8. Center for Drug Evaluation and Research (CDER) March 2003 BP.

9. Drug Products General Considerations (USFDA – CDER, March 2003.
10. Drugs and Cosmetics Act. (First Amendment) Rules, 2013, dated 30th January 2013.
11. Guidance for Industry–Bioavailability and Bioequivalence Studies for orally administrated drug.
12. Guidance for Industry – Statistical Approaches to establishing Bioequivalence (USFDA –CDER, January 2002.
13. ICH Guideline "Statistical Principles for Clinical Trial" Step 4, 1998.
14. LC-MS/MS Bioanalysis Method Development, Validation, and Sample Analysis: Points to Consider When Conducting Nonclinical and Clinical Studies in Accordance with Current Regulatory Guidance.
15. The European Medicines Agency ICH Topic E 6 (R1) Guideline for Good 25-Clinical U.S. Department of Health and Human Services Food and Drug Administration.
16. Shah VP, Midha KK, Dighe S, McGilveray IJ, Skelly JP, Yacobi A, Layloff T, Viswanathan CT, Cook CE, McDowall RD, Pittman KA. (1992) Analytical methods validation: bioavailability, bioequivalence, and pharmacokinetic studies. Journal of Pharmaceutical Sciences.81(3):309-12.
17. Ni J, Ouyang H, Aiello M, Seto C, Borbridge L, Sakuma T, Ellis R, Welty D, Acheampong A.(2008) Micro dosing assessment to evaluate pharmacokinetics and drug metabolism in rats using liquid chromatography-tandem mass spectrometry. Pharmaceutical research. 25(7):1572-82.
18. Ni W, McNaughton L, LeMaster DM, Sinha R, Turesky RJ. (2007) Quantitation of 13 heterocyclic aromatic amines in cooked beef, pork, and chicken by liquid chromatography-electrospray ionization/tandem mass spectrometry. Journal of agricultural and food chemistry. 56(1):68-7.