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# The rate and Extent of absorption of oral Meptazinol 200 mg on healthy volunteer

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ABSTRACT

Meptazinol is a centrally acting analgesic belonging to the hexahydro-azepine series, which has demonstrated mixed agonist and antagonist activity at opioid receptors.Receptor binding studies have shown that although meptazinol displays only a low affinity for μ and k opioid receptor sites, it has a some what higher affinity for the subpopulation of μ sites. These binding sites also displays a high affinity for the endogenous opioid peptides, and are thought to be responsible for, among other things, analgesia, but not for the mediation of respiratory depression. A component of its analgesic action is also attributable, in mice at least, to an effect on central cholinergic transmission. In this respect it differs from all conventional analgesic drugs which have been examined (1).Based on this information this drug requires no blocking of opioid receptor during the bioequivalence study. But to achieve the highest degree of safety, close monitoring will be performed to detect the occurrence of any side effect, As well as Anarchole 50mg tablets (Naltrexone, the opioid blocker) will be available at the emergency drugs store to treat any opioid side effect.



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## Introduction

This study was a comparative single-dose, open-label, randomized, two-treatment, two-sequence, two-period, crossover, in-vivo study to determine the bioequivalence of Meptaless 200mg Film Coated Tablet (Meptazinol 200 mg) , versus Meptid 200mg Film Coated Tablets (Meptazinol 200 mg) after a single dose administration given to healthy adult volunteers under fasting conditions. The subjects who conform to the study entry criteria were dosed according to a randomization schedule. The study was designed and completed according to the good clinical and laboratory practices (2,3). To investigate single-dose bioequivalence of treatment A; Meptaless 200 mg Film Coated Tablet (Meptazinol 200 mg) and treatment B; Meptid 200 mg Film Coated Tablets (Meptazinol 200 mg) given to healthy adult volunteers under fasting conditions. For the ln-transformed ratio (test product/reference product) for the bioequivalence parameters (Cmax, AUC0-t, and AUC0-∞) while other pharmacokinetic parameters of ke, t1/2, Tmax, and (AUC0-t/AUC0-∞) % were reported. The influence of sequence, product, and period effect were tested by ANOVA.

## Ethics Considerations

This research will be carried out in accordance with conditions stipulated by international clinical research guidelines and the principles enunciated in the Declaration of Helsinki resolved in Helsinki in 1964s and amended in Scotland, 2000; and the ICH harmonized tripartite guideline regarding Goo Clinical Practice (GCP) adopted by the European Agency for the Evaluation of Medicinal Products (5). In addition, all local regulatory requirements will be adhered to, in particular those which afford greater ion to the study of the participants

## 1. Dosage forms and strengths

### 1.1. Methods and Procedures

On study day 1 of each study period, the study drugs were administered according to a randomization plan.

**Treatment A**: One Meptaless 200 mg Film Coated Tablet taken (Meptazinol 200 mg) with 240 mL of water (measured with a 300-mL cylinder) at room temperature.

**Treatment B**: One Meptid 200 mg Film Coated Tablets (Meptazinol 200 mg) taken with 240 mL of water (measured with a 300-mL cylinder) at room temperature.

**Subjects Assignment in the Study**

Twenty-four volunteering subjects are required to fully complete the two periods of the study, which is expected to be sufficient to obtain a statistical power adequate for the Assessment of average bioequivalence. The subjects will be selected, from the Egyptian population, healthy volunteers, 18-55 years of age, weighing at least 45 kg and their body mass index (BMI) of 18 – 30 (inclusive both) kg/m2.

| | |
|---|---|
| **AIM of the Study** | Evaluation by comparing the bioavailability and therefore, the bioequivalence of two different formulations of Meptazinol after a single oral dose administration, under fasting conditions. |
| **Methodology** | Eligible subjects received test and reference products as a single oral dose on two different occasions. Blood samples were collected at zero (0) time Pre-dose, 0.- 24 hours after dosing. Meptazinol concentrations in blood samples were determined by a validated LC.MS.MS assay method. |
| **Statistical Methods** | The statistical analysis was performed according to the method of Schuirmann (1987) *. The assessment of bioequivalence between the test and the reference products was based on the ratios of the mean pharmacokinetic parameter .The Bioequivalence (BE) was concluded if either tail probability did not exceed the 90 % confidence limit and was completely contained in the 0.80 - 1.25 ranges for $AUC_{0-t}$, $AUC_{0-\infty}$ and in the 0.80 -1.25 range for $C_{max}$. Analysis of variance (ANOVA) is performed on pharmacokinetic parameters AUCs, $T_{max}$ & $C_{max}$. |
| **Results** | Oral administration of Test Product: Meptaless ( Meptazinol 200 mg ) to healthy volunteer showed No effect on blood pressure as compared by the Reference Product : Meptid( Meptazinol 200 mg ) ,which increase the blood pressure by 3.23 %. |
| **Conclusion** | The Test product, Meptaless 200mg Film Coated Tablet by Penta pharma Egypt is bioequivalent to the reference drug, Meptid®200mg Film Coated Tablets |

**Disposition of Volunteers**

Healthy subjects were recruited according to the selection criteria described in the study protocol and volunteered for months prior to the first study drug administration of study period I)

- Number of Screened Volunteers 33
- Number of Enrolled Volunteers 33
- Number of volunteers who completed period I 33

participation in the study. All participating subjects were treated as a single group.

Each subject was examined thoroughly during screening procedure (the screening time being set to be not more than two months prior to the first study drug administration of study period I)months prior to the first study drug administration of study period I)

- Number of volunteers who completed period II 31
- Number of Withdrawn Volunteers 2*
- Number of Excluded Volunteers 1**

33

33

33

**1.2. Dietary Restrictions, Standardized Diet and Fluid Intake**

No consumption of alcohol was permitted for the subjects 48 hours prior to the study's drugs administration until the collection of the last sample of the respective study period. No consumption of any beverages or foods containing methylxanthines, e.g., caffeine (coffee, tea, cola, cocoa, chocolate, etc.) was permitted for the subjects 12 hours prior to the study's drugs administration until the collection of last blood sample of the respective study period **(7).**

**1.3. Collection and Handling of Blood Samples for Analysis:**

In the morning of study day 1 of each study period and before study's drugs administration, a cannula was inserted into the subject's forearm vein and it remained there until the last blood sample was collected.

The volume of blood taken for the determination of Meptazinol in plasma was 5 mL per sample. The following blood samples for the analysis of Meptazinol in plasma were collected: at the following intervals: 0(pre-dose) 0.16, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours after dosing. The number of blood collections for drug analysis was 18 samples in each study period.

Blood samples were collected into tubes containing heparin as an anticoagulant slightly shaken and centrifuged at approximately 3500 rpm for 10 minutes **(8).**

After centrifugation, plasma samples were transferred directly into a 5-mL plastic tube. These samples were immediately stored at the study site in an ultradeep freezer at a nominal temperature of -80 °C.

**2. Bio-analytical Drug Determination Methodology:**

Meptazinol in human plasma. Samples from the subjects (who completed all periods of the study) were analyzed **(9).** The bio-analytical method was validated according to the international guidelines. Details of the validation of the assay procedure are given in section 5 "Bio-analytical Method & Validation" **(10,11,12).**

**3. Pharmacokinetic Calculations**

The pharmacokinetic parameters of Meptazinol were estimated using standard non-compartmental methods **(4).**

The maximal plasma concentration was taken directly from the measured data. The area under the plasma concentration–time curve (AUCt) was calculated from measured data points from the time of administration to the time of last quantifiable concentration (Clast) by the linear trapezoidal rule **(13,14).**

The area under the plasma concentration–time curve extrapolated to infinity (AUC∞) was calculated according to the following formula:

AUC0-∞ = AUC0-t + Clast / [ln (2)/t½], where Clast is the last quantifiable concentration.

The ratio AUC0-t/AUC0/-∞ as a percent was determined as an indicator for the adequacy of sampling time.

The elimination half-life t½ was calculated as t½ = ln (2)/(-b) where b was obtained as the slope of the linear regression of the ln-transformed plasma concentrations versus time in the terminal period of the plasma curve.

**4. Statistical Analysis**

The statistical analysis was performed according to the method of Schuirmann (1987) * **(6).** The assessment of bioequivalence between the test and the reference products was based on the ratios of the mean pharmacokinetic parameter AUC0-t, AUC0-∞, Cmax, Tmax & t1/2. The Bioequivalence (BE) was concluded if either tail probability did not exceed the 90 % confidence limit and was completely contained in the 0.80 - 1.25 ranges for AUC0-t, AUC0-∞ and in the 0.80 -1.25 range for Cmax. Analysis of variance (ANOVA) is performed on pharmacokinetic parameters AUCs, Tmax & Cmax.

Statistical analysis was performed by a validated Kinetica version 5.1 software.

**4.1 .Descriptive Statistics**

Descriptive Statistics, including the means, standard deviations and pharmacokinetic parameters, arithmetic means, standard deviations, coefficient of variation, geometric means and ratio of means shall be reported.

**4.2. Analyses of Variance (ANOVA)**

Analyses of variance will be performed on the ln-transformed pharmacokinetics parameters AUC0-∞, AUC0-t and Cmax. The analysis of variance model will include sequence; subjects nested within sequence, period and drug formulation as factors, employing 5% level of significance of the sequence effect will be tested using the subjects nested within sequence, as the error term.

**4.3. Wilcoxon test**

A Wilcoxon signed-rank test (aka Wilcoxon matched-pairs test) was used to determine if there is a significant difference between the Tmax values of the test product and the reference product.

**5. Confidence Intervals and Bioequivalence Evaluation**

Consistent with two one-sided tests for bioequivalence, 90% confidence intervals for the difference between drug formulation means will be calculated for the ln-transformed parameters AUC0-t, AUC0-∞ and Cmax.

The confidence intervals will be expressed as a percentage relative to the means of reference formulation. The geometric mean values for the (test/reference) ratios of AUC0-t, AUC0-∞ and Cmax will be reported to define the point estimate. The confidence intervals of ln-transformed (test/reference) ratios for AUC0-t, AUC0-∞ and Cmax are to be within 80.00-125.00%.

**Reagents, Chemicals & Standards:**

- Meptazinol hydrochloride working standard (potency 100.1%, loss on drying: 0.2%)

- Paracetamol working standard (potency 99.8%, water content; 0.20%)

- Water for chromatography (Sharlau, Spain)

- Isopropanol HPLC grade (fisher chemicals), Acetonitrile, HPLC grade (Sigma Aldrich Chemie GmbH, Steinheim-Germany)

- Butyl methyl ether, (M-Tedia)

- Blank plasma obtained from the Holding Company for Biological Products & Vaccines (VACSERA), Giza, Egypt

**Discussion**

Bioequivalence evaluation is usually carried out by comparing the in vivo rate and extent of drug absorption of a test and reference formulation in healthy subjects. Study participants received test and reference products on separate occasions, in single dose, with random assignment to the three possible sequences of product administration.

Plasma samples were analyzed for drug concentrations, and pharmacokinetic parameters were obtained from the resulting concentration-time curves. These pharmacokinetic parameters were then analyzed statistically to determine whether the test and reference products yielded comparable values. Standard statistical methodology based on the two one-sided tests procedure to determine whether average values for pharmacokinetic parameters measured after administration of the test and reference products are comparable.

This procedure involves the calculation of a 90% confidence interval for the ratio (or difference) between the test and reference product pharmacokinetic variable averages. The limits of the observed confidence intervals were within a predetermined range for the ratio (or difference) of the product averages. The determination of the confidence interval range and the statistical level of significance based on parametric (normal theory) standard non-compartmental procedures was employed for the analysis of pharmacokinetic data derived from *in vivo* bioequivalence studies. ANOVA was performed on the pharmacokinetic parameters to assess the effect of variables [subject (sequence), subject, period, and formulation] on the study outcome. On the basis of these considerations, a single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study on healthy normal subjects was adopted.

**Statistical results : Tables (1-11)**

**Table (1): Adverse Effect of oral administration of both Test Product: Meptaless ( Meptazinol 200 mg ) and the Reference Product( Meptazinol 200 mg ).**

Oral administration of Test Product: Meptaless to healthy volunteer showed No effect on blood pressure as compared by the Reference Product : Meptid ,which increase the blood pressure by 3.23 %.

Oral administration of both Test Product: Meptaless and the Reference Product : Meptid to healthy volunteer showed No cardiovascular side

effect .

| Studies Body System / Adverse Event | Reported Incidence by Treatment Groups | |
|---|---|---|
| | Fasted Bioequivalence Study | |
| | Test | Reference |
| Body as a whole | 0.00% | 0.00% |
| Dizziness | 3.23% | 0.00% |
| Headache | 6.67% | 3.23% |
| Nausea | 3.23% | 0.00% |
| Vomiting. | 3.23% | 0.00% |
| Cardiovascular | 0.00% | 0.00% |
| Hypotension | 0.00% | 0.00% |
| Hypertension | 0.00% | 3.23% |
| Gastrointestinal | 9.68% | 0.00% |
| Abdominal pain | 0.00% | 0.00% |
| Allergic reaction | 0.00% | 0.00% |
| Other organ systems | 0.00% | 0.00% |
| Total % | 26.04% | 6.46% |

**A- Plasma Concentration-Time Profiles for Each Volunteer**

**Table (2):** Plasma concentration levels of Meptazinol (ng/mL) following administration of single oral dose of Treatment (B) reference product Meptid 200mg Film Coated Tablets

**Note: letter M indicates missed samples**

**B- Tables of Pharmacokinetic Parameters**

**Table 3:** Pharmacokinetic parameters of Meptazinol following administration of single oral dose of test product (A) Meptaless 200mg Film Coated Tablet to 30 volunteers

| | **0** | **0.166667** | **0.25** | **0.5** | **0.75** | **1** | **1.25** | **1.5** | **1.75** | **2** | **2.5** | **3** | **4** | **6** | **8** | **10** | **12** | **24** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 0 | 6.19 | 20 | 23.1 | 70.9 | 56 | 45.9 | 52.7 | 41.2 | 37 | 55.3 | 42 | 31.2 | 30.6 | 34 | 17.9 | 7.77 | 16 |
| **2** | 0 | 48.4 | 7.35 | 8.69 | 51.3 | 42.1 | 39.3 | 41.1 | 61.6 | 34 | 63.6 | 43 | 19.7 | 13.7 | 10.5 | 7.96 | 12.4 | 6.24 |
| **3** | 0 | 11.6 | 9.8 | 65.7 | 46.1 | 31 | 29.7 | 37.2 | 23.2 | 18.9 | 14.8 | 23.6 | 13.5 | 9.88 | 17.8 | 8.95 | 5.85 | 6.71 |
| **4** | 0 | 0 | 8.14 | 14.8 | 25.6 | 31.8 | 25.4 | 39.3 | 24.3 | 23.5 | 19.5 | 19.6 | 11.3 | 8.99 | 9.82 | 10.2 | 5.61 | 0 |
| **5** | 0 | 4.59 | 5.33 | 27.5 | 19.7 | 13 | 38.4 | 13.1 | 17 | 16.9 | 9.69 | 10.2 | 8.9 | 6.9 | 6.27 | 7.65 | 2.13 | 6.92 |
| **6** | 0 | 29.7 | 59.7 | 14.9 | 4.16 | 3.59 | 3.59 | 15.1 | 7.48 | 11.2 | 18 | 14 | 9.97 | 7.46 | 5.97 | 4.71 | 6.11 | m |
| **7** | 0 | 5.74 | 43.8 | 19 | 32.9 | 43.2 | 35.9 | 30.1 | 20.8 | 15.7 | 30.5 | 16.7 | 20.3 | 10.8 | 19.6 | 8.89 | 22.9 | 7.93 |
| **8** | 0 | 17.7 | 14.8 | 5.19 | 13 | 33.4 | 27 | 23.7 | 20.2 | 21.5 | 66.4 | 22.3 | 13.8 | 7.33 | 10.4 | 5.31 | 15.3 | 19.3 |
| **9** | 0 | 4.92 | 6.67 | 21.4 | 19.2 | 37.9 | 35.1 | 41.2 | 43.1 | 41.4 | 35.9 | 33.7 | 18.7 | 8.46 | 8.15 | 7.9 | 14.9 | 15.9 |
| **10** | 0 | 5.53 | 6.53 | 14.8 | 25.9 | 33.5 | 27.3 | 28.8 | 18.8 | 20 | 14.3 | 13.3 | 10.4 | 8.83 | 8.41 | 6.2 | 7.73 | 5.15 |
| **11** | 0 | 13.2 | 24.2 | 22.9 | 71 | 72.6 | 50.8 | 44.5 | 36.5 | 30.8 | 31.8 | 34.1 | 25.9 | 42.4 | 16 | 9.23 | 8.67 | 8.31 |
| **12** | 0 | 8.3 | 20 | 34.2 | 19.7 | 24.9 | 26.5 | 23.5 | 28.6 | 17.9 | 16.7 | 13.9 | 12.1 | 9.92 | 5.39 | 6.64 | 7.82 | 5.18 |
| **13** | 0 | 0 | 21.8 | 16.6 | 22.2 | 28.1 | 33.2 | 39.7 | 43.6 | 39.1 | 20.3 | 17.9 | 11.3 | 11.2 | 8.43 | 5.78 | 6.59 | 5.24 |
| **14** | 0 | 7.24 | 8.62 | 14.1 | 27.8 | 43.5 | 41.9 | 44.7 | 49 | 43.2 | 47.8 | 23.6 | 23 | 10.1 | 8.34 | 7.72 | 20.1 | 10.9 |
| **15** | 0 | 0 | 0 | 2.51 | m | 30.2 | 12.9 | 12.9 | 10 | m | 9.15 | 8.83 | 2.68 | 0 | 3.65 | 0 | m | m |
| **17** | 0 | 0 | 5.22 | 10 | 20.1 | 13.7 | 10.1 | 7.78 | 7.1 | 8.24 | 4.97 | 4.84 | 5.62 | 0 | 0 | 0 | 0 | 0 |
| **18** | 0 | 20 | 13.2 | 34.1 | 15.9 | 15.6 | 23.3 | 21.8 | 54.3 | 56.6 | 40.9 | 36.3 | 27.1 | 15.9 | 19 | 12.1 | 6.1 | 5.69 |
| **19** | 0 | 6.96 | 18 | 15.5 | 26.1 | 43.6 | 41.2 | 46.2 | 51.2 | 36.8 | 59.7 | 27.3 | 17.2 | 11.7 | 17.2 | 12.7 | 8.29 | 14.7 |
| **20** | 0 | 15.8 | 13.9 | 14.1 | 26 | 31.7 | 39.8 | 31.6 | 31.4 | 24.3 | 20.6 | 15.9 | 14.6 | 10.2 | 12.2 | 7.65 | 6.98 | 14.2 |
| **21** | 0 | 2.53 | 6.33 | 54.6 | 66.7 | 62.5 | 73.6 | 20 | 36.5 | 32.7 | 32.1 | 33.2 | 16 | 9.09 | 5.23 | 9.48 | 0 | m |
| **22** | 0 | 0 | 0 | 14.8 | 56.4 | 25.7 | 20 | 25 | 22.3 | 47.3 | 16.9 | 11.3 | 10.7 | 4.23 | 5.2 | 0 | 4.37 | 6.49 |
| **23** | 0 | 4.68 | 58.7 | 11.5 | 68.1 | 17.7 | 17.8 | 11.4 | 4.48 | 19.9 | 11 | 15 | 29.9 | 7.51 | 1.65 | 0 | 0 | 0 |
| **24** | 0 | 0 | 0 | 10.1 | 16.2 | 24.1 | 22.7 | 19.8 | 16.2 | 14.9 | 18.3 | m | 6.61 | 0 | 0 | 0 | 0 | 0 |
| **25** | 0 | 0 | 23.3 | 48.1 | 42.7 | 57.6 | 48.9 | 40.3 | 32.4 | 30.3 | 16.2 | 16.3 | 9.91 | 0 | 1.66 | 0 | 0 | 0 |
| **26** | 0 | 0 | 0 | 12.4 | 17.1 | 22.1 | 24.2 | 22.1 | 15.9 | 4.09 | 10.5 | 10.3 | 4.33 | 3.82 | 4.86 | 6.8 | 0 | 0 |
| **27** | 0 | 0 | 0 | 23.4 | 18.1 | 20.5 | 26 | 18.6 | 17.7 | 22.7 | 15.7 | 11.1 | 6.76 | 1.79 | 0 | 0 | 9.32 | 0 |
| **28** | 0 | 0 | 32.1 | 43.2 | 36.6 | 23.8 | 28.6 | 23.7 | 24.2 | 24.8 | 16.1 | 13.2 | 6.56 | 3.39 | 0 | 0 | 0 | 0 |
| **29** | 0 | 0 | 0 | 0 | 7.55 | 8.71 | 23.6 | 34.9 | 52.9 | 29.3 | 22.8 | 19.9 | 14.7 | 6.87 | 12 | 0 | 0 | 0 |
| **30** | 0 | 0 | 3.64 | 8.73 | 7.01 | 9.11 | 10.3 | 8.11 | 14.6 | 5.13 | 7.01 | 3.43 | 0 | 0 | 0 | 0 | 9.12 | 0 |
| **33** | 0 | 12 | 15.3 | 32.7 | 38.3 | 47.9 | 53.1 | 41.4 | 44.5 | 39.8 | 29.8 | 26.7 | 9.92 | 9.52 | 3.29 | 2.14 | 3.6 | 0 |

| Vol no. | Period | Cmax (ng/mL) | Tmax (hr) | AUC0-t (ng.hr/mL) | AUCExt (ng.hr/mL) | AUC0-∞ (ng.hr/mL) | % AUCExt | Ke (hr-1) | t1/2 (hr) |
|---|---|---|---|---|---|---|---|---|---|
| **1** | II | 54.5000 | 1.5000 | 182.3970 | 30.9953 | 213.3920 | 14.5251 | 0.1567 | 4.4222 |
| **2** | I | 65.1000 | 1.5000 | 320.6940 | 4.7920 | 325.4860 | 1.4723 | 0.1650 | 4.2013 |
| **3** | I | 40.1000 | 0.5000 | 155.5170 | 33.8024 | 189.3200 | 17.8547 | 0.1537 | 4.5094 |
| **4** | II | 44.2000 | 1.5000 | 342.1930 | 9.0297 | 351.2230 | 2.5709 | 0.1265 | 5.4799 |
| **5** | I | 26.2000 | 4.0000 | 143.0250 | 25.1798 | 168.2040 | 14.9698 | 0.1660 | 4.1762 |
| **6** | II | 23.7000 | 1.0000 | 94.9746 | 0.0673 | 95.0419 | 0.0708 | 0.2948 | 2.3514 |
| **7** | II | 40.5000 | 0.7500 | 454.9070 | 21.3082 | 476.2150 | 4.4745 | 0.1114 | 6.2236 |
| **8** | I | 80.2000 | 1.7500 | 602.1470 | 0.0295 | 602.1770 | 0.0049 | 0.3576 | 1.9385 |
| **9** | II | 67.9000 | 1.2500 | 322.4270 | 4.7300 | 327.1570 | 1.4458 | 0.1737 | 3.9910 |
| **10** | I | 27.9000 | 1.7500 | 162.6880 | 6.9224 | 169.6100 | 4.0814 | 0.1368 | 5.0687 |
| **11** | II | 68.7000 | 0.7500 | 305.6910 | 1.9616 | 307.6520 | 0.6376 | 0.2308 | 3.0034 |
| **12** | I | 31.7000 | 1.7500 | 255.5670 | 10.5101 | 266.0780 | 3.9500 | 0.1434 | 4.8350 |
| **13** | I | 54.8000 | 1.5000 | 269.8070 | 11.0582 | 280.8660 | 3.9372 | 0.1251 | 5.5429 |
| **14** | I | 53.7000 | 1.2500 | 324.8560 | 6.3529 | 331.2090 | 1.9181 | 0.1598 | 4.3364 |
| **15** | II | 21.4000 | 0.2500 | 24.4029 | 3.8449 | 28.2478 | 13.6114 | 0.5861 | 1.1826 |
| **17** | I | 15.9000 | 2.0000 | 40.2775 | 6.7013 | 46.9788 | 14.2644 | 0.3240 | 2.1396 |
| **18** | I | 76.8000 | 1.7500 | 655.0670 | 23.4163 | 678.4830 | 3.4513 | 0.1284 | 5.4002 |
| **19** | II | 65.0000 | 2.0000 | 292.2500 | 84.1414 | 376.3910 | 22.3548 | 0.1249 | 5.5487 |
| **20** | II | 21.3000 | 2.0000 | 307.3190 | 75.7458 | 383.0650 | 19.7736 | 0.0779 | 8.9009 |
| **21** | II | 39.1000 | 1.5000 | 112.5610 | 5.5916 | 118.1520 | 4.7326 | 0.3855 | 1.7980 |
| **22** | I | 39.8000 | 1.5000 | 166.6160 | 6.5299 | 173.1460 | 3.7713 | 0.1286 | 5.3887 |
| **23** | II | 35.1000 | 0.5000 | 159.9510 | 56.6609 | 216.6120 | 26.1578 | 0.0894 | 7.7510 |
| **24** | I | 48.3000 | 1.0000 | 104.8910 | 5.8482 | 110.7390 | 5.2811 | 0.5403 | 1.2829 |
| **25** | II | 42.6000 | 1.2500 | 108.9400 | 17.1301 | 126.0700 | 13.5878 | 0.2164 | 3.2031 |
| **26** | I | 73.8000 | 1.0000 | 136.2350 | 5.9811 | 142.2160 | 4.2056 | 0.2924 | 2.3706 |
| **27** | I | 49.3000 | 1.2500 | 107.1620 | 20.9319 | 128.0940 | 16.3410 | 0.2562 | 2.7050 |
| **28** | II | 26.1000 | 0.7500 | 59.9025 | 10.0887 | 69.9912 | 14.4142 | 0.3406 | 2.0348 |
| **29** | I | 62.4000 | 0.7500 | 253.2050 | 4.8420 | 258.0470 | 1.8764 | 0.3723 | 1.8618 |
| **30** | II | 48.9000 | 1.7500 | 75.9933 | 38.7098 | 114.7030 | 33.7478 | 0.1200 | 5.7773 |
| **33** | II | 72.7000 | 1.7500 | 134.4550 | 10.1462 | 144.6010 | 7.0167 | 0.2195 | 3.1578 |
| **average** | | 47.2567 | 1.3917 | 222.5373 | 18.1016 | 240.6389 | 9.2167 | 0.2235 | 4.0194 |
| **SD** | | 18.2604 | 0.6791 | 150.5425 | 20.8573 | 153.0769 | 8.5578 | 0.1264 | 1.8726 |
| **Cv%** | | 38.6410 | 48.7978 | 67.6482 | 115.2231 | 63.6127 | 92.8514 | 56.5447 | 46.5895 |

**Table (4) :** Pharmacokinetic parameters of Meptazinol following administration of single oral dose of reference product (B) Meptid 200mg Film Coated Tablets 30 volunteers

| Vol no. | Period | $C_{max}$ (ng/mL) | $T_{max}$ (hr) | $AUC_{0-t}$ (ng.hr/mL) | $AUC_{Ext}$ (ng.hr/mL) | $AUC_{0-\infty}$ (ng.hr/mL) | % $AUC_{Ext}$ | $K_e$ ($hr^{-1}$) | $t_{1/2}$ (hr) |
|---|---|---|---|---|---|---|---|---|---|
| **1** | I | 70.9000 | 0.7500 | 511.7720 | 0.2595 | 512.0320 | 0.0507 | 0.3690 | 1.8783 |
| **2** | II | 63.6000 | 2.5000 | 363.2070 | 4.9844 | 368.1920 | 1.3537 | 0.1748 | 3.9644 |
| **3** | II | 65.7000 | 0.5000 | 268.2160 | 0.7146 | 268.9300 | 0.2657 | 0.2782 | 2.4916 |
| **4** | I | 39.3000 | 1.5000 | 155.4990 | 48.1395 | 203.6390 | 23.6397 | 0.1231 | 5.6310 |
| **5** | II | 38.4000 | 1.2500 | 163.8900 | 4.2468 | 168.1360 | 2.5258 | 0.1411 | 4.9139 |
| **6** | I | 59.7000 | 0.2500 | 106.9120 | 18.4927 | 125.4050 | 14.7464 | 0.1667 | 4.1573 |
| **7** | I | 43.8000 | 0.2500 | 404.0650 | 0.5981 | 404.6630 | 0.1478 | 0.2407 | 2.8798 |
| **8** | II | 66.4000 | 2.5000 | 382.9690 | 9.6729 | 392.6420 | 2.4635 | 0.1364 | 5.0802 |
| **9** | I | 43.1000 | 1.7500 | 386.7220 | 7.4616 | 394.1830 | 1.8929 | 0.1522 | 4.5554 |
| **10** | II | 33.5000 | 1.0000 | 211.1700 | 14.9972 | 226.1670 | 6.6310 | 0.1014 | 6.8349 |
| **11** | I | 72.6000 | 1.0000 | 417.9430 | 10.0038 | 427.9470 | 2.3376 | 0.1487 | 4.6614 |
| **12** | II | 34.2000 | 0.5000 | 217.0780 | 0.9810 | 218.0590 | 0.4499 | 0.2087 | 3.3211 |
| **13** | II | 43.6000 | 1.7500 | 233.0610 | 10.2419 | 243.3030 | 4.2095 | 0.1220 | 5.6806 |
| **14** | II | 49.0000 | 1.7500 | 408.3120 | 10.4242 | 418.7360 | 2.4895 | 0.1424 | 4.8677 |
| **15** | I | 30.2000 | 1.0000 | 43.7275 | 13.1431 | 56.8706 | 23.1106 | 0.2077 | 3.3377 |
| **17** | II | 20.1000 | 0.7500 | 30.0800 | 10.2158 | 40.2958 | 25.3521 | 0.3756 | 1.8453 |
| **18** | II | 56.6000 | 2.0000 | 326.3400 | 0.7389 | 327.0790 | 0.2259 | 0.2840 | 2.4403 |
| **19** | I | 59.7000 | 2.5000 | 379.1750 | 5.1925 | 384.3670 | 1.3509 | 0.1825 | 3.7988 |
| **20** | I | 39.8000 | 1.2500 | 295.3390 | 15.0618 | 310.4010 | 4.8524 | 0.1125 | 6.1640 |
| **21** | I | 73.6000 | 1.2500 | 195.1790 | 24.5635 | 219.7420 | 11.1783 | 0.2205 | 3.1439 |
| **22** | II | 56.4000 | 0.7500 | 180.1530 | 1.2900 | 181.4420 | 0.7110 | 0.1975 | 3.5094 |
| **23** | I | 68.1000 | 0.7500 | 128.8460 | 2.3295 | 131.1750 | 1.7759 | 0.7243 | 0.9570 |
| **24** | II | 24.1000 | 1.0000 | 56.1200 | 17.9671 | 74.0871 | 24.2514 | 0.4053 | 1.7102 |
| **25** | I | 57.6000 | 1.0000 | 119.5960 | 3.6390 | 123.2350 | 2.9529 | 0.4540 | 1.5269 |
| **26** | II | 24.2000 | 1.2500 | 73.6137 | 3.0834 | 76.6972 | 4.0202 | 0.3120 | 2.2216 |
| **27** | II | 26.0000 | 1.2500 | 78.8025 | 33.9149 | 112.7170 | 30.0884 | 0.1237 | 5.6023 |
| **28** | I | 43.2000 | 0.5000 | 90.8550 | 6.6259 | 97.4809 | 6.7971 | 0.4716 | 1.4697 |
| **29** | II | 52.9000 | 1.7500 | 117.0180 | 32.2864 | 149.3040 | 21.6246 | 0.2286 | 3.0324 |
| **30** | I | 14.6000 | 1.7500 | 32.1929 | 0.0016 | 32.1945 | 0.0048 | 0.8749 | 0.7923 |
| **33** | I | 53.1000 | 1.2500 | 166.7550 | 5.6084 | 172.3630 | 3.2538 | 0.2992 | 2.3164 |
| **average** | | 47.4667 | 1.2417 | 218.1536 | 10.5627 | 228.7162 | 7.4918 | 0.2660 | 3.4929 |
| **SD** | | 16.5221 | 0.6208 | 135.9857 | 11.2551 | 133.1687 | 9.2333 | 0.1762 | 1.6109 |
| **Cv%** | | 34.8078 | 49.9944 | 62.3348 | 106.5559 | 58.2244 | 123.2448 | 66.2386 | 46.1190 |

**Table 5:** Plasma concentration Average ± SD (ng/mL) of Meptazinol following oral administration of Treatment (A) test product Meptaless 200 mg Film Coated Tablet and Treatment

(B) reference product Meptid 200 mg Film Coated Tablets 30 volunteers

| Time (hr.) | **Meptaless 200 mg Film Coated Tablet** | | **Meptid 200 mg Film Coated Tablets** | |
|---|---|---|---|---|
| | Average | ± SD | Average | ± SD |
| 0.0 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| 0.17 | 8.6643 | 11.3423 | 7.5027 | 10.6623 |
| 0.25 | 12.8762 | 9.7194 | 14.8810 | 15.9205 |
| 0.5 | 17.3993 | 11.8776 | 21.2873 | 15.4597 |
| 0.75 | 24.4883 | 16.8128 | 31.4593 | 19.8467 |
| 1.0 | 30.8927 | 17.4132 | 31.6370 | 16.7173 |
| 1.25 | 28.8590 | 14.8282 | 31.2030 | 14.7255 |
| 1.5 | 34.7170 | 15.3844 | 28.6763 | 12.6298 |
| 1.75 | 31.7847 | 18.4767 | 29.0353 | 15.7455 |
| 2.0 | 25.4193 | 12.0150 | 26.4814 | 12.9152 |
| 2.5 | 21.6323 | 10.3329 | 25.8773 | 17.3481 |
| 3.0 | 18.7353 | 10.8750 | 20.0517 | 10.6540 |
| 4.0 | 15.6960 | 9.2060 | 13.7553 | 7.9191 |
| 6.0 | 10.7280 | 9.9432 | 9.0197 | 8.7620 |
| 8.0 | 9.4433 | 8.8248 | 8.5007 | 7.6544 |
| 10.0 | 7.1259 | 6.9964 | 5.5303 | 4.8007 |
| 12.0 | 6.9670 | 7.6268 | 6.6090 | 6.0822 |
| 24.0 | 4.9643 | 6.7238 | 5.7356 | 6.0407 |

**Table (6):** Mean values of the pharmacokinetic parameters of Meptazinol derived from the plasma concentration-time profiles of test (A) product Meptaless 200mg Film Coated Tablet and reference (B) Product Meptid 200mg Film Coated Tablets following single oral administration of 200 mg Meptazinol to 30 healthy volunteers

| | **Test A** | | | **Reference B** | | |
|---|---|---|---|---|---|---|
| | Average | SD | CV% | Average | SD | CV% |
| **Cmax (ng/mL)** | 47.2567 | 18.2604 | 38.6410 | 47.4667 | 16.5221 | 34.8078 |
| **Tmax (hr)** | 1.3917 | 0.6791 | 48.7978 | 1.2417 | 0.6208 | 49.9944 |
| **AUC0-t (ng.hr/mL)** | 222.5373 | 150.5425 | 67.6482 | 218.1536 | 135.9857 | 62.3348 |
| **AUCExt (ng.hr/mL)** | 18.1016 | 20.8573 | 115.2231 | 10.5627 | 11.2551 | 106.5559 |
| **AUC0-∞ (ng.hr/mL)** | 240.6389 | 153.0769 | 63.6127 | 228.7162 | 133.1687 | 58.2244 |
| **AUCExt/ AUC0-∞** | 9.2167 | 8.5578 | 92.8514 | 7.4918 | 9.2333 | 123.2448 |
| **Ke (hr-1)** | 0.2235 | 0.1264 | 56.5447 | 0.2660 | 0.1762 | 66.2386 |
| **t1/2 (hr)** | 4.0194 | 1.8726 | 46.5895 | 3.4929 | 1.6109 | 46.1190 |

**Table (7):** 90% Confidence Interval & Point Estimate for Cmax, AUC0-t & AUC0-∞

| | **Point Estimate** | **Lower Confidence Limit** | **Upper Confidence Limit** |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 98.42% | 84.41% | 114.76% |
| $AUC_{0-t}$ (ng.hr/mL) | 103.23% | 89.82% | 118.66% |
| $AUC_{0-\infty}$ (ng.hr/mL) | 105.13% | 91.3% | 121.06% |

**C-ANOVA Tables for the Pharmacokinetic Parameters**

**Table (8):** ANOVA table with Confidence Interval for Ln Cmax

| SOURCE | D.F | SS | MS | F | p |
|---|---|---|---|---|---|
| Period | 1 | 0.259501 | 0.259501 | 2.12291 | 0.1562 |
| Subject (Seq) | 28 | 6.89307 | 0.246181 | 2.01394 | 0.03455 |
| Formulation | 1 | 0.00377699 | 0.00377699 | 0.0308986 | 0.8617 |
| Sequence | 1 | 0.0162592 | 0.0162592 | 0.133012 | 0.7181 |
| Error | 28 | 3.42267 | 0.122238 | | |
| Total | 59 | 10.5953 | | | |

**Table (9):** ANOVA table with Confidence Interval for Ln AUC0-t

| SOURCE | D.F | SS | MS | F | p |
|---|---|---|---|---|---|
| Period | 1 | 0.328507 | 0.328507 | 3.27044 | 0.08129 |
| Subject (Seq) | 28 | 31.5735 | 1.12763 | 11.226 | 4.296e-009 |
| Formulation | 1 | 0.0152352 | 0.0152352 | 0.151673 | 0.6999 |
| Sequence | 1 | 0.134758 | 0.134758 | 1.34158 | 0.2565 |
| Error | 28 | 2.81253 | 0.100447 | | |
| Total | 59 | 34.8645 | | | |

**Table (10):** ANOVA table with Confidence Interval for Ln AUC0-inf

| SOURCE | D.F | SS | MS | F | p |
|---|---|---|---|---|---|
| Period | 1 | 0.161075 | 0.161075 | 1.56185 | 0.2217 |
| Subject (Seq) | 28 | 27.4746 | 0.981235 | 9.51448 | 2.978e-008 |
| Formulation | 1 | 0.0375467 | 0.0375467 | 0.364069 | 0.5511 |
| Sequence | 1 | 0.0831092 | 0.0831092 | 0.805863 | 0.377 |
| Error | 28 | 2.88766 | 0.103131 | | |
| Total | 59 | 30.644 | | | |

**Table (11): Wilcoxon T test (Non-parametric test for $T_{max}$)**

| Wilcoxon T test: |
|---|
| Difference between the two groups: |
| delta (1) = -0.75 |
| delta (2) = 1 |
| delta (3) = 0 |
| delta (4) = 0 |
| delta (5) = -2.75 |
| delta (6) = -0.75 |
| delta (7) = -0.5 |
| delta (8) = 0.75 |
| delta (9) = 0.5 |
| delta (10) = -0.75 |
| delta (11) = 0.25 |
| delta (12) = -1.25 |
| delta (13) = 0.25 |
| delta (14) = 0.5 |
| delta (15) = 0.25 |
| delta (16) = 0.5 |
| delta (17) = -0.75 |
| delta (18) = -1.25 |
| delta (19) = -0.75 |
| delta (20) = 0.25 |
| delta (21) = 0 |
| delta (22) = -0.25 |
| delta (23) = 0.25 |
| delta (24) = 0 |
| delta (25) = -0.25 |
| delta (26) = 1 |
| delta (27) = 0 |
| delta (28) = -0.5 |
| delta (29) = 0.75 |
| delta (30) = -0.25 |

M = 192.5; P = 132.5; Sigma P = 1381.25; Epsilon P = 0.807207

Epsilon Paired Table > 0.05: 0.41955>0.05

The difference is not significant.

**Figures : (1-12)**

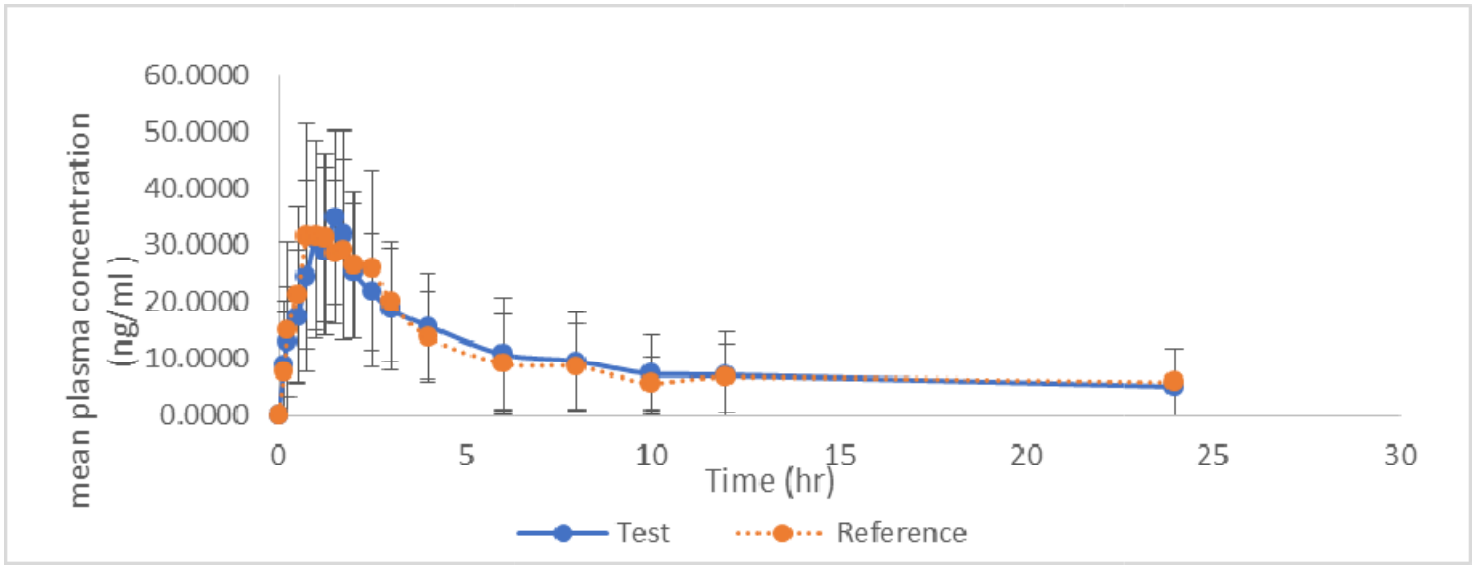


**Figure 1 :** Mean plasma concentration vs time profile for Meptazinol after administration of an oral single-dose of 200 mg Meptazinol of the test product (Meptaless 200mg Film Coated Tablet) and the reference product (Meptid 200 Film Coated Tablets)

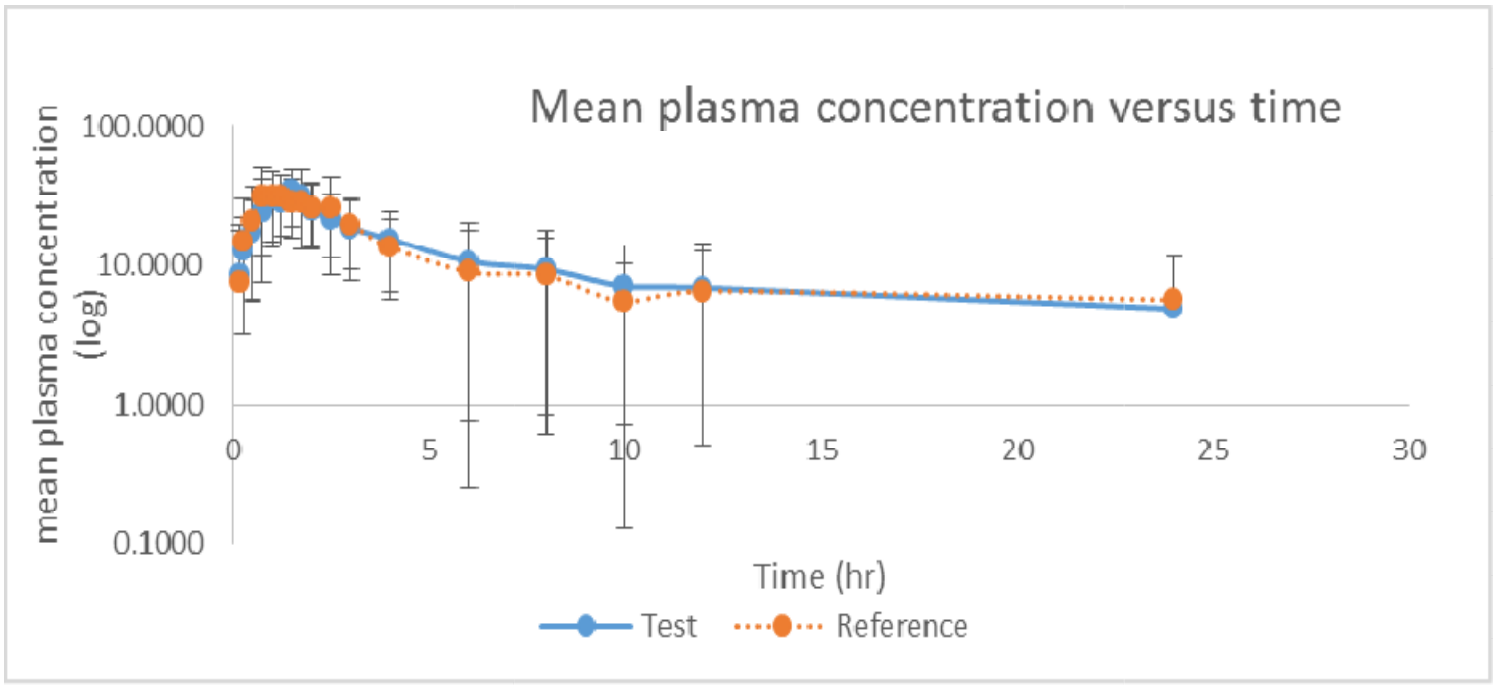


**Figure 2 :** Logarithmic mean plasma concentration vs time profile for Meptazinol after administration of an oral single-dose of 200 mg Meptazinol of the test product (Meptaless 200mg Film Coated Tablet) and the reference product (Meptid 200 Film Coated Tablets)

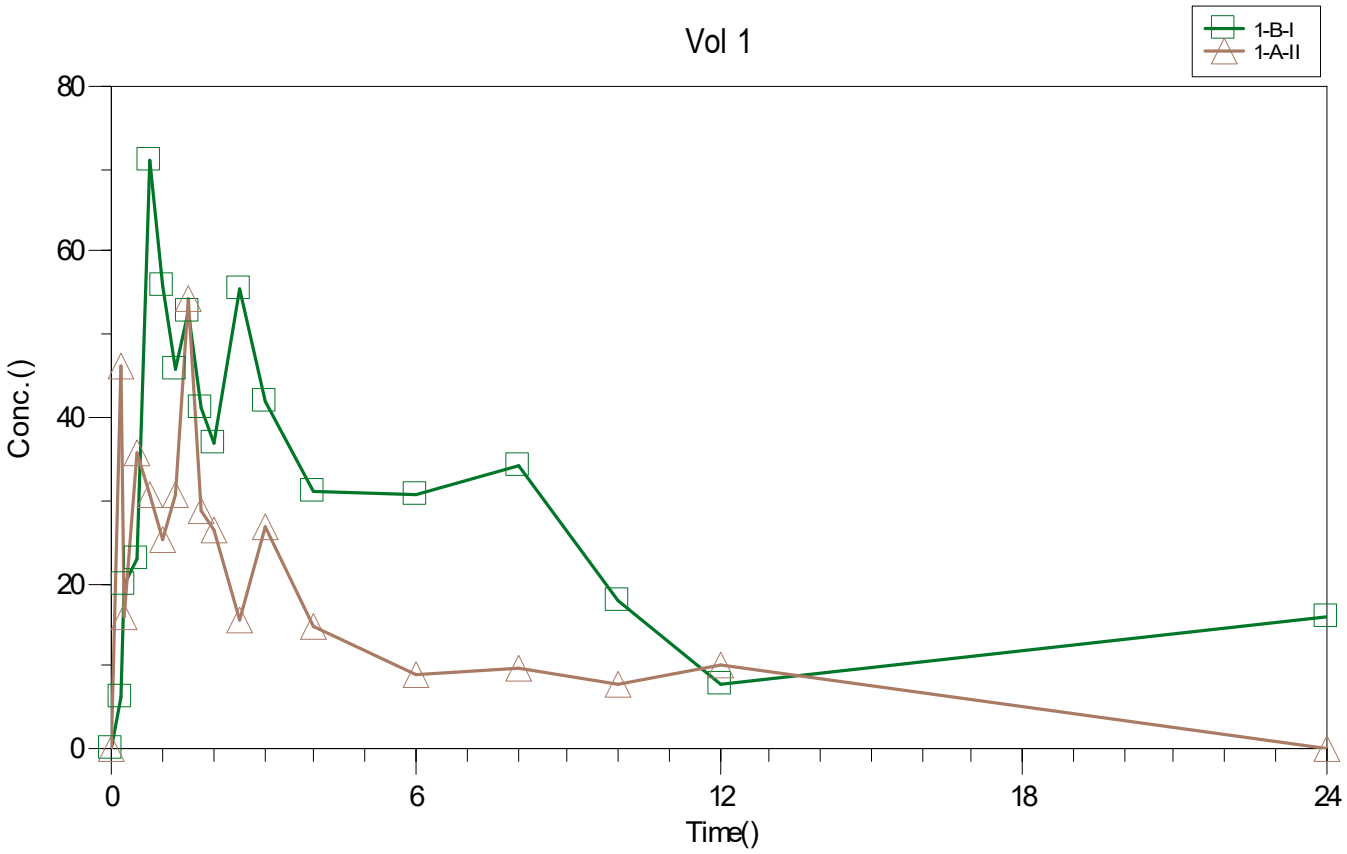


**Figure 3:** Concentration (ng/ml) versus time (hours) plot of volunteer 1 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

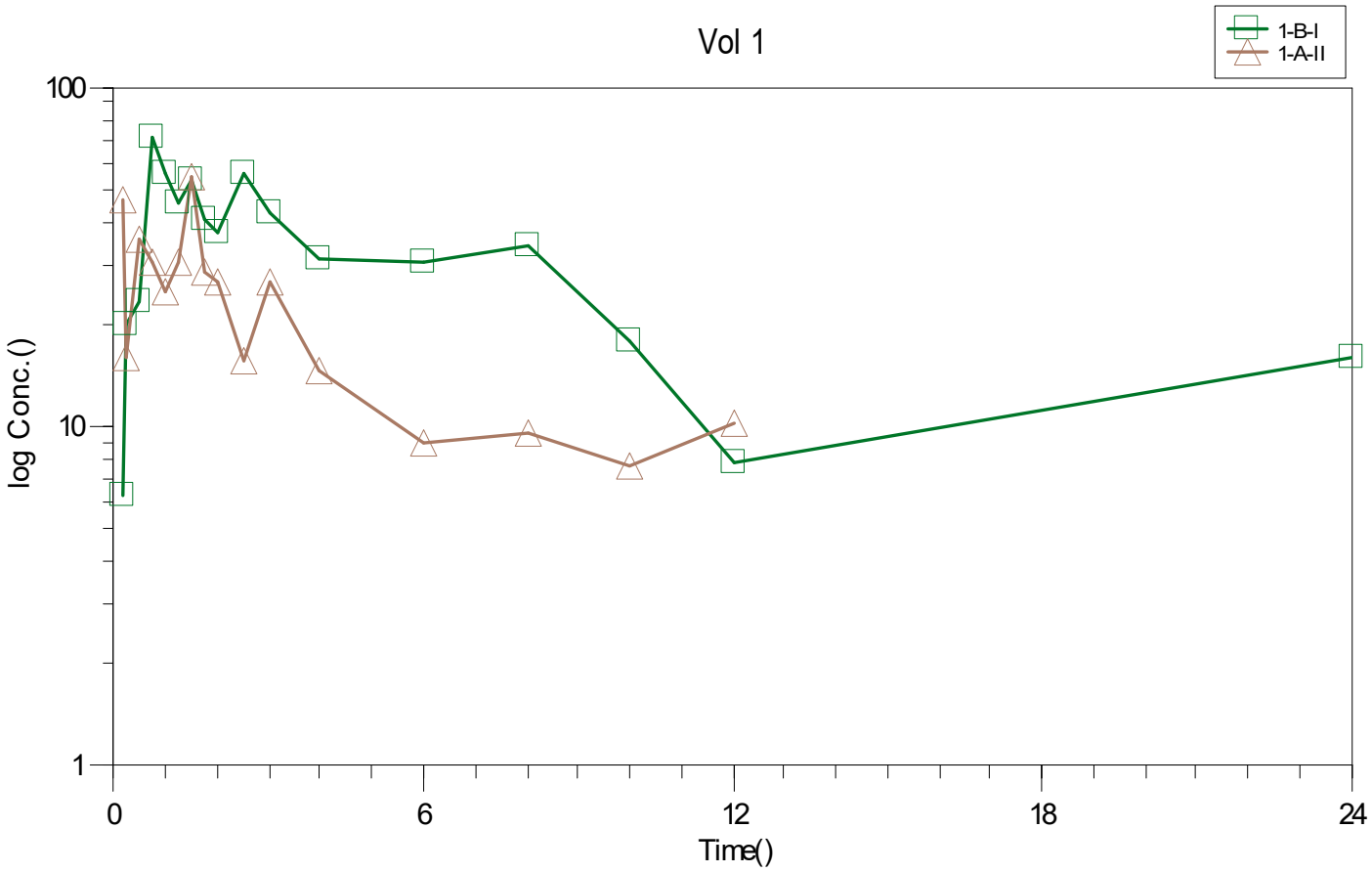


**Figure 4:** log concentration (ng/ml) versus time (hours) plot of volunteer 1 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

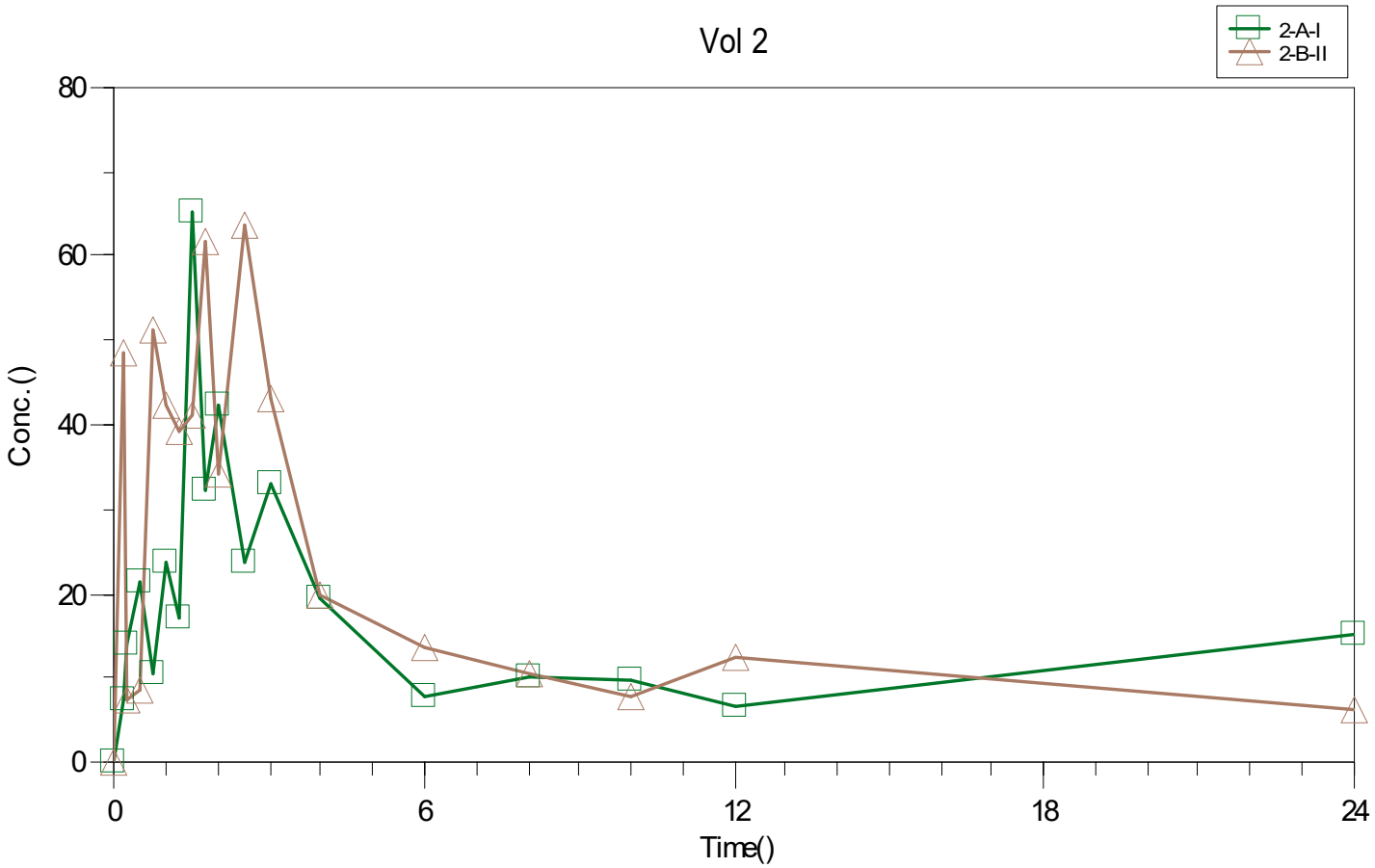


**Figure 5:** Concentration (ng/ml) versus time (hours) plot of volunteer 2 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

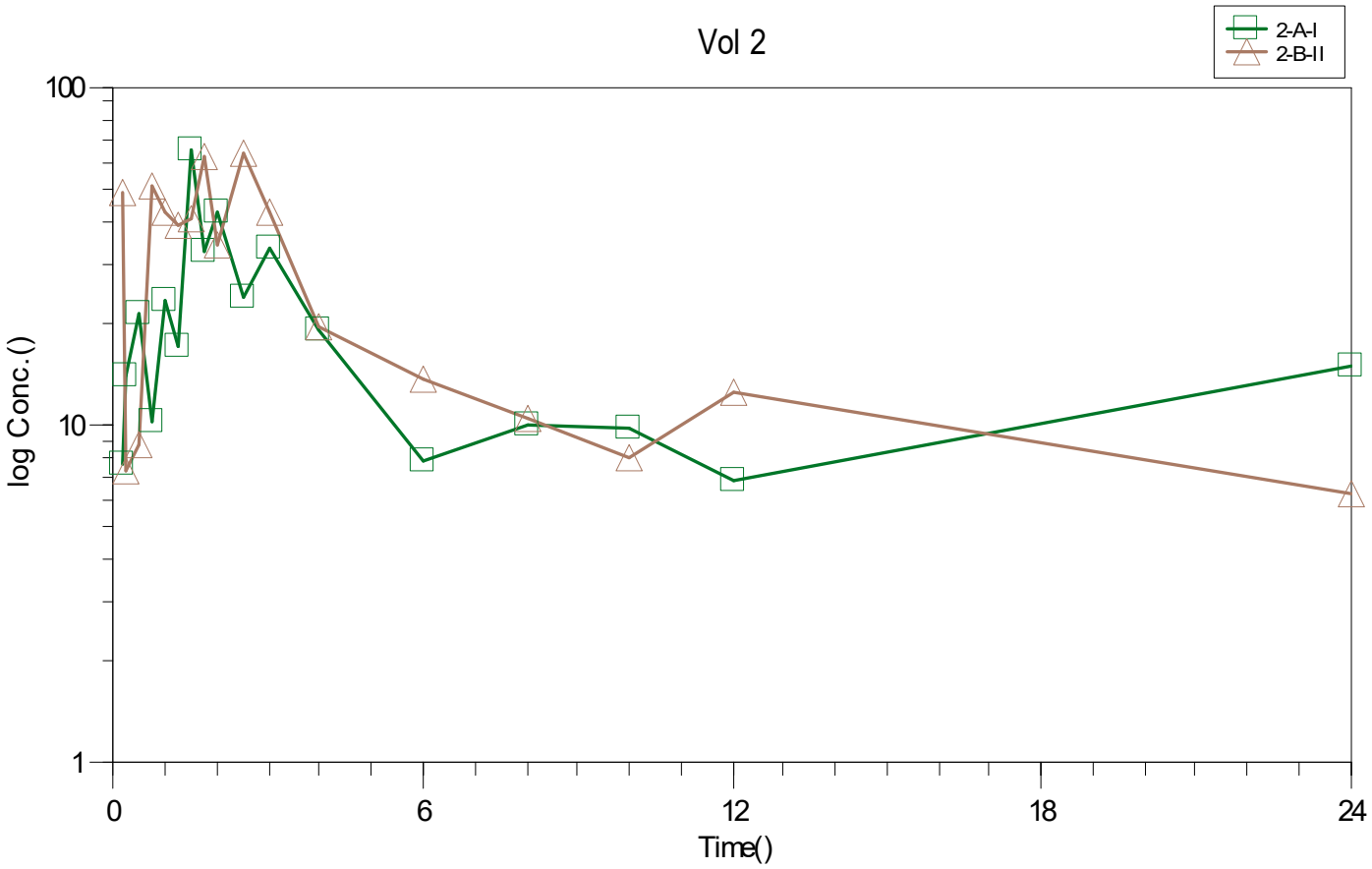


**Figure 6:** Log concentration (ng/ml) versus time (hours) plot of volunteer 2 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

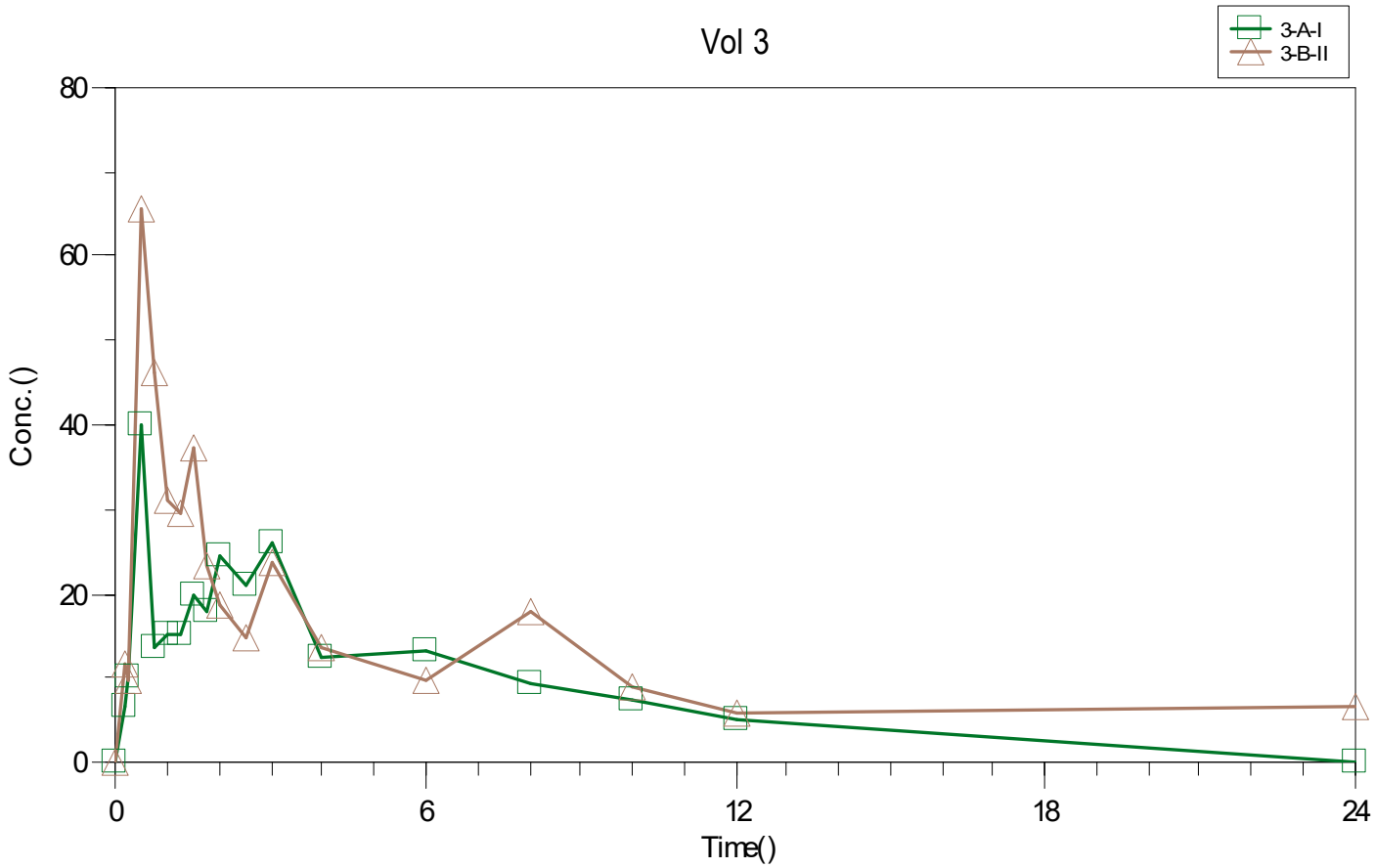


**Figure 7:** Concentration (ng/ml) versus time (hours) plot of volunteer 3 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

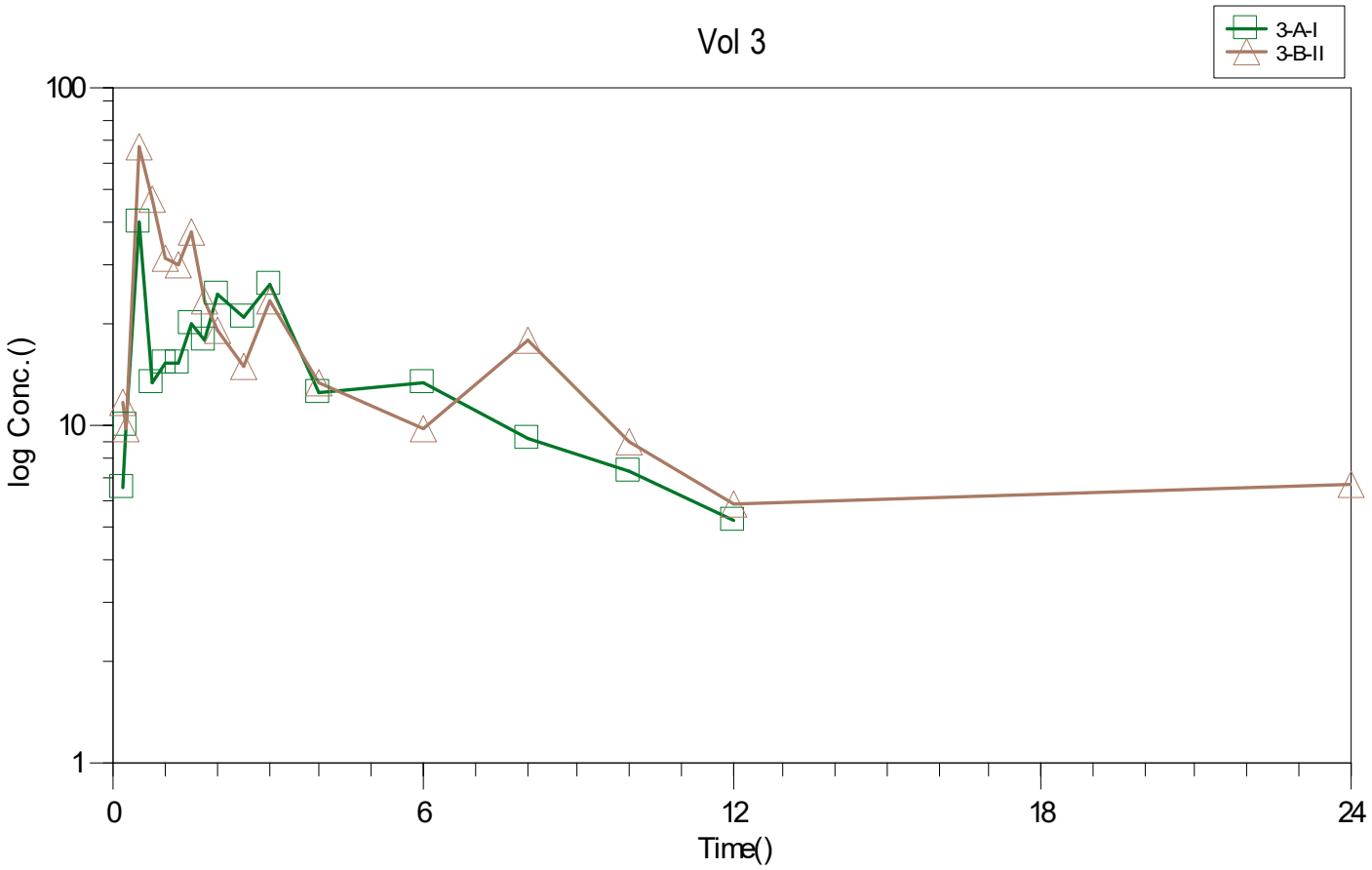


**Figure 8 :** Log concentration (ng/ml) versus time (hours) plot of volunteer 3 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

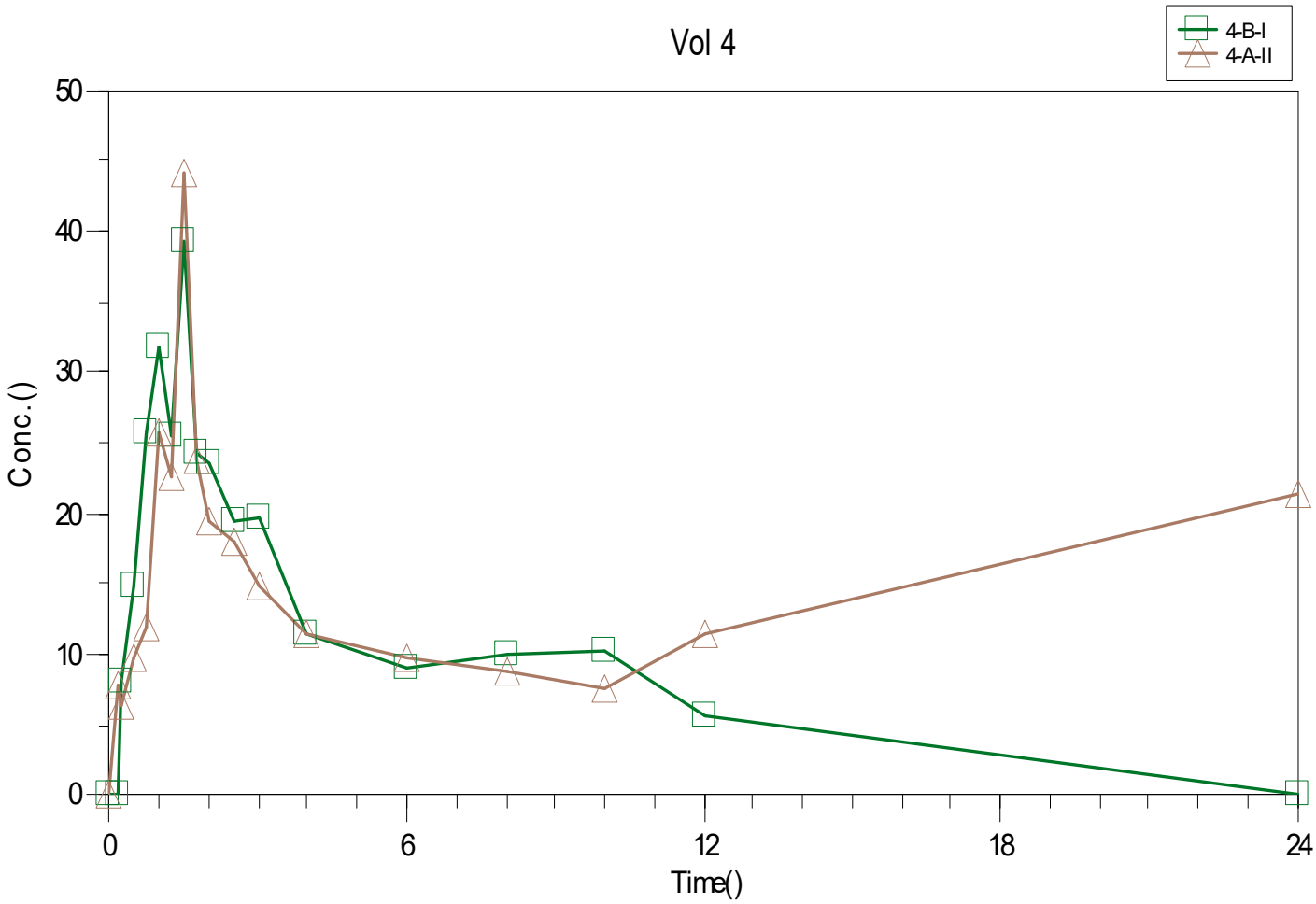


**Figure 9:** Concentration (ng/ml) versus time (hours) plot of volunteer 4 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

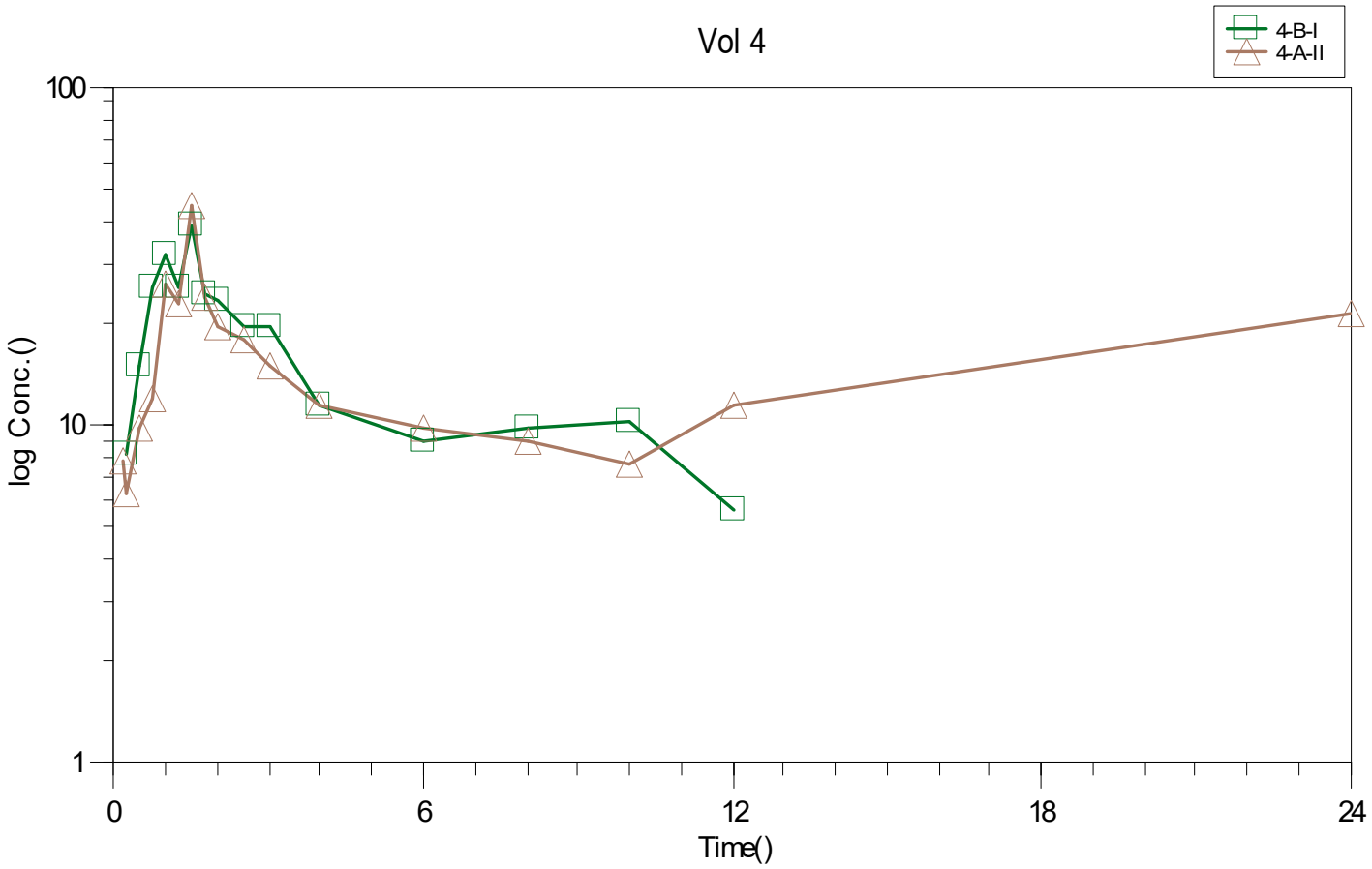


**Figure 10:** Log concentration (ng/ml) versus time (hours) plot of volunteer 4 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

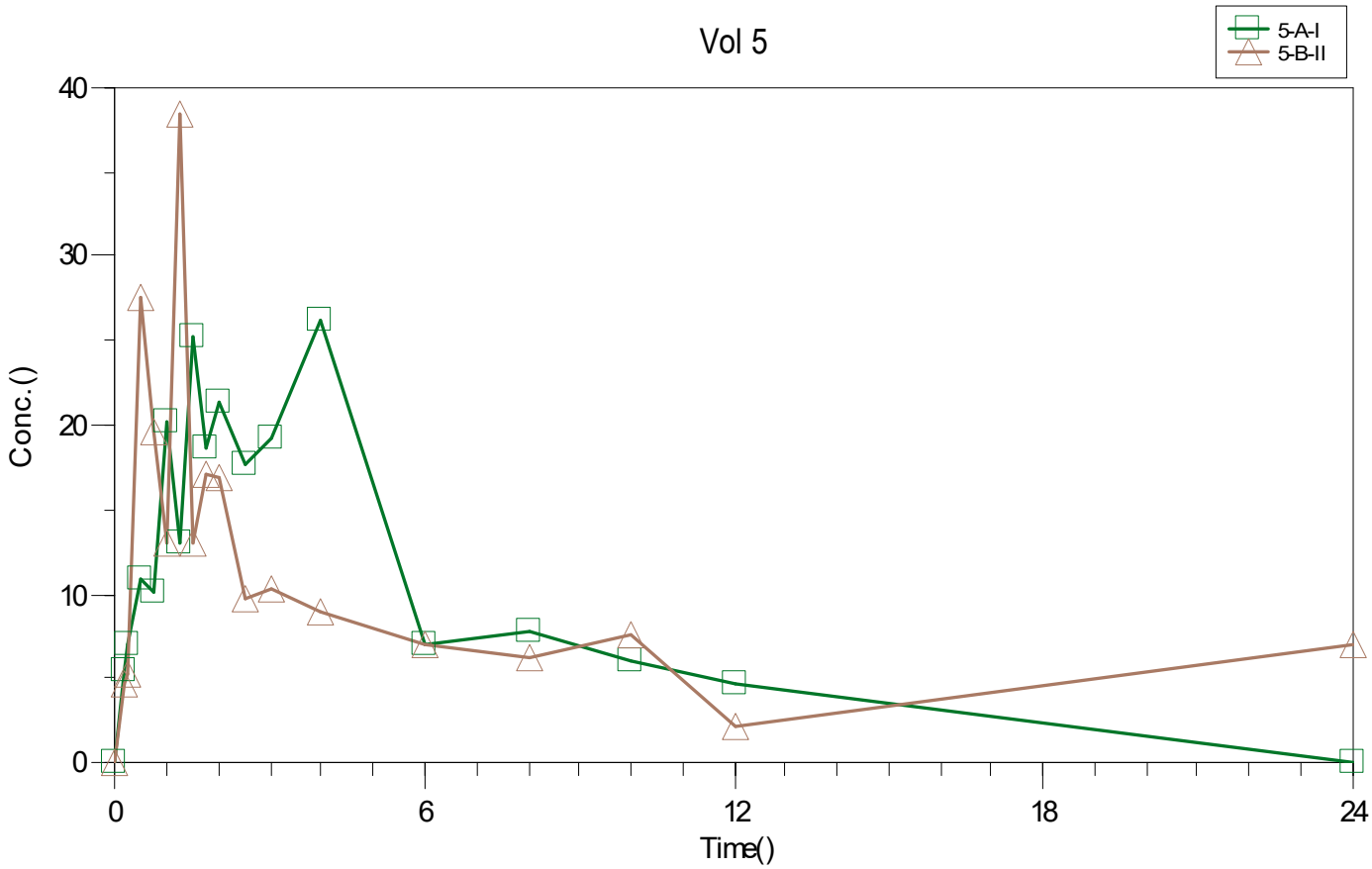


**Figure 11:** Concentration (ng/ml) versus time (hours) plot of volunteer 5 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

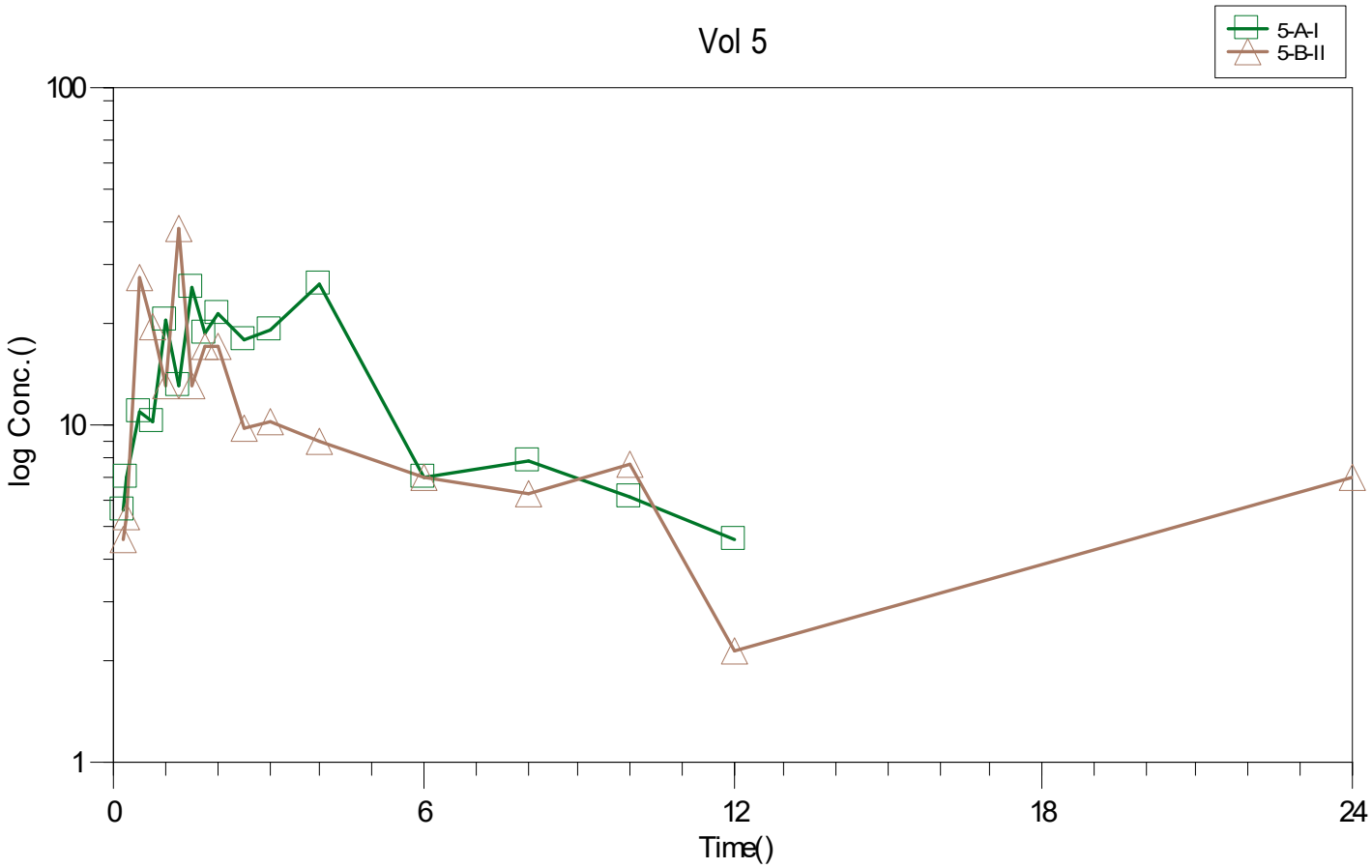


**Figure 12:** Log concentration (ng/ml) versus time (hours) plot of volunteer 5 after single dose drug administration of test (A) Meptaless 200 mg Film coated tablets and reference (B) Meptid 200 mg Film coated tablets

**Conclusion**

Bioequivalence could be demonstrated for Meptazinol within the prescribed 90% confidence interval of 80.00% to 125.00% for AUC0-t and AUC0-∞ and for Cmax to be within 80.00% to 125.00% with respect to the parametric method on ln-transformed data.

Oral administration of Test Product: Meptaless ( Meptazinol 200 mg ) to healthy volunteer showed No effect on blood pressure as compared by the Reference Product : Meptid( Meptazinol 200 mg ) ,which increase the blood pressure by 3.23 %.

Oral administration of both Test Product: Meptaless ( Meptazinol 200 mg ) and the Reference Product : Meptid( Meptazinol 200 mg ) to healthy volunteer showed No effect on cardiovascular .

The test product, Meptaless 200mg Film Coated, investigated in this study was shown to be bioequivalent with the reference product; Meptid 200 mg Film Coated Tablets .

Plasma levels may be used as surrogate parameters for therapeutic response.

Therefore, the data obtained in this study prove, by appropriate statistical methods, the essential similarity of plasma levels of Meptazinol from the test product Meptaless 200 mg Film Coated Tablet and from the reference product Meptid 200 mg Film Coated Tablets suggesting equal clinical efficacy of these two products.

The product, Meptaless 200mg Film Coated Tablet , may be used interchangeably with the reference product Meptid 200mg Film Coated Tablets . That was shown the tested product has an acceptable therapeutic efficacy.

**References**

1. Goldstuck ND.; Ward PJ. Treatment of pain following IUD insertion with meptazinol--a new centrally acting analgesic. *Contracept Deliv Syst.* 1983, 4, 33-37.
2. Zheng W.; Li J.; Qiu Z.; Xia Z.; Li W.; Yu L.; Chen H.; Chen J.; Chen Y.; Hu Z.; Zhou W.; Shao B.; Cui Y.; Xie, Q. Novel bis-(-)-nor-meptazinol derivatives act as dual binding site AChE inhibitors with metal-complexing property. *Toxicol Appl Pharmacol.* 2012, 264, 65-72.
3. Shi Z.; Zhang Q.; Jiang X. Pharmacokinetic behavior in plasma, cerebrospinal fluid and cerebral cortex after

intranasal administration of hydrochloride meptazinol. *Life Sci.* 2005, 77, 2574-2583.

4. Rosseel MT, Bogaert MG, Belpaire FM. Meptazinol (Wy 22811), a new analgesic: preliminary pharmacokinetic data. *Curr Med Res Opin*. 1975, 3, 181-186.
5. "Declaration of Helsinki." As amended by the 52nd World Medical Assembly (WMA). World Medical Association, Edinburgh, Scotland, October 2000.
6. Schuirmann, D. J. "A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability." *J Pharmacokinet Biopharm*. 1987, 15(6), 657-680.
7. "EEC-note for Guidance" Investigation on Bioavailability and Bioequivalence.
8. Eurachem Guide. The Fitness for Purpose of Analytical Methods. A Laboratory Guide to Method Validation and Related Topics, 1998.
9. The Fitness for Purpose of Analytical Methods. A Laboratory Guide to Method Validation and Related Topics. Eurachem Guide, 1998.
10. Guidance for Industry: Statistical approaches to Establishing Bioequivalence. U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Centre for Drug Evaluation and Research (CDER), January 2001.
11. Guidance for Industry: FDA Bioanalytical Method Validation Guidelines U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Centre for Drug Evaluation and Research (CDER), May 2001.
12. Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations. U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Centre for Drug Evaluation and Research (CDER), March 2003.
13. International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guidelines for Good Clinical Practice. May 1996.
14. USP24-NF-19. The United States Pharmacopeia -The National Formulary *In vivo* Bioequivalence Guideline., United States Pharmacopeial Convention, Inc.: Rockville, MD, 2001.