5.0 DISCUSSION

The rising cost of health care has motivated governments around the world to examine methods of decreasing costs without compromising health care services. One of the methods to reduce costs, employed by many countries is the passing of regulations that encourage the use of generic drugs. Generic drugs are typically less expensive than brand-name drugs. Many nations throughout the world have come to rely on low-cost, good-quality multi-source (generic) pharmaceutical products as means of providing lower healthcare costs without sacrificing important public health goals. (Henry, 2006).

The present study was undertaken to launch a generic version of Olmesartan which could replace safely & successfully innovator drug product (OLMETEC®40). Hence, the pharmacokinetic bioequivalence of two batches of olmesartan medoxomil 40 mg tablet manufacture by Ranbaxy Laboratories Limited were evaluated using OLMETEC®40 mg film coated tablet (containing 40 mg olmesartan medoxomil) manufactured by Daiichi Sankyo UK Ltd, as Reference product R, following single dose oral administration in healthy, adult, male human subjects under fasting conditions.

In the present study, first a liquid chromatography mass spectrometric (LC-MS/MS) method was developed and validated for the analysis of Olmesartan in plasma. In second step the formulations were administered in study comprising of 12 healthy, adult, male, human, subjects under fasting condition & followed by estimation of Olmesartan in human plasma using the validated liquid chromatography mass spectrometric (LC-MS/MS) assay. Pharmacokinetic parameters AUC_{0-inf}, AUC_{0-t}, AUC_{%Extrap}, C_{max}, T_{max}, K_{el}, T_{1/2} were calculated for Olmesartan using WinNonlin-Node version 5.0.1. A statistical analysis was performed on plasma Olmesartan using the SAS system.

A chromatographic method was developed and validated for selectivity, sensitivity, recovery, ruggedness, and stabilities. Between batch precision and accuracy ranged from 1.6% to 3.4% and 97.6% to 104.4% respectively. These results were within the acceptance limit of ≤15% and ±15% for precision and accuracy as per guidelines.

Similar results for precision and accuracy were obtained in method developed & validated by (Raja and Lakshmana, 2011). Between batch precision and accuracy in this study ranged from 1.9% to 3.9% and 98.0% to 102.0% respectively.
For Olmesartan & Olmesartan-d4 (ISTD) selectivity using Six lots of normal human plasma, one lot of haemolysed human plasma and one lot of lipemic plasma, with K3EDTA as an anticoagulant were evaluated and none showed significant interfering peaks at the retention time. Recovery of analyte Olmesartan & Olmesartan-d4 (ISTD) found to be 75.7 and 80.2 % respectively. All other results of validation parameters were in acceptable range as per regulatory guidelines. The method was therefore reliable, reproducible, accurate and validated for the purpose of this study.

Kinetic profile in the present study revealed that maximum concentration mean (C_{max}) in plasma after Olmesartan administration was attained by test formulation B 1392.94 (ng/ml) which was in close proximity to C_{max} of Olmesartan reference formulation R i.e. 1408.65 (ng/ml), whereas the C_{max} achieved by the test formulation A was 1313.13 ng/ml which was lower than formulations B & R. Both test formulation A & B having value of C_{max} lower than reference formulation. Reason for low C_{max} can be concluded due to sample size constraint, high intrasubject variability (28.6) or formulation difference. This was a pilot study carried out with low sample size (12) to evaluate test formulation in comparison of innovator. Generally, pilot studies are conducted to validate analytical methodology, assess variability and to optimize sample collection time interval. Smaller the size of pilot study, the more uncertain the outcomes.

In relation to the reference formulation and Test product B the values obtained for test product A were lower with respect to area under the curve. As mean AUC_{0-\infty} for formulations A, B and R were 9143.89, 9342.59, 9338.36 ng.hr/ml, and mean AUC_{0-\infty} were 9385.82, 9567.54, 9533.43 ng.hr/ml respectively [Table 4.1 A]. These results demonstrated that the bioavailability of test formulation A & B was lower than the reference formulation, however, test formulation B shows better bioavailability as compared to test formulation A.

Kun-Yan Li et.al conduct a study in 2010 investigated the relative bioavailability and fasting pharmacokinetic properties of olmesartan after single doses of a 20-mg test tablet, a 20-mg test capsule, and a commercially available 20-mg reference tablet in healthy Chinese male volunteers. The study was conducted to satisfy Chinese State Food and Drug Administration regulatory requirements for approval of a generic formulation of olmesartan medoxomil. Blood samples were obtained at baseline and at 0.5, 1, 1.5, 2, 2.5,3,4,6,8,12,24,36, and 48 hours after dosing. The value of C_{max} found for tests and reference formulation were 495.0, 396.0, and 530.0 (ng/ml) respectively.
The value of AUCₜ₀⁻, AUCₜ₀⁻∞ were 3993, 3567, 3849 and 3091, 2956 ng.hr/ml respectively. Results of this study conclude that formulations of olmesartan medoxomil 20-mg capsules and tablets met the regulatory criteria for assuming bioequivalence. The bioequivalence in this study was achieved because of large sample size (28) and low intrasubject variability. Hence to achieve bioequivalence we need to conduct current study on a large sample size.

The A/R (%) ratios for log transformed data for the pharmacokinetic parameters Cₘₐₓ, AUCₜ₀⁻, AUCₜ₀⁻∞ were 90.03, 97.11, and 98.31 respectively. The 90% confidence intervals for log transformed data for Cₘₐₓ, AUCₜ₀⁻, and AUCₜ₀⁻∞ for the test product A vs. reference R (A/R) were 73.09-110.90, 83.73-112.62, and 85.94-112.47 respectively [Table 4.19 A]. With the exception of Cmax both of the area under curve value was within the stated regulatory bioequivalence range of 80-125% (FDA, DCGI). Therefore, it can be concluded that test product A is not bioequivalent to reference product R.

The B/R (%) ratios for log transformed data for the pharmacokinetic parameters Cₘₐₓ, AUCₜ₀⁻, and AUCₜ₀⁻∞ were 97.00, 100.77 and 101.15 respectively. The 90% confidence intervals for log transformed data for parameters Cₘₐₓ, AUCₜ₀⁻, and AUCₜ₀⁻∞ for the test product B vs. reference R (B/R) were 78.75-119.49, 86.89-116.87 and 88.42-115.71 respectively [Table 4.19B]. For the product B with the exception of Cₘₐₓ both of the area under curve value was within the stated regulatory bioequivalence range of 80-125% (FDA, DCGI). Therefore, it can be concluded that test product B is not bioequivalent to reference product R.

Based on the above results it can be concluded that product A and product B are not bioequivalent to product R, as per US: FDA and DCGI 80-125% criteria.

The intra subject variability for the Cₘₐₓ, AUCₜ₀⁻, and AUCₜ₀⁻∞ was reported for log-transformed data. Overall, the intrasubject variability (expressed as % CV) for all the products was less than 30%. Intra subject variability was 28.6, 20.2, and 18.3 for Cmax, AUCₜ₀⁻, and AUCₜ₀⁻∞ respectively [Table 4.19 C].

P values were calculated for the pharmacokinetic parameters Cₘₐₓ, AUCₜ₀⁻, and AUCₜ₀⁻∞. There was no period and sequence effect as indicated by the p values shown in Table (4.30 C) (p values for these effects >0.05 from the ANOVA model). High p value indicates that there was no period and sequence effect.
Power of the test for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> was found to be 40.46%, 69.18%, and 77.61% respectively [Table 4.19 C]. The power of test was less than 80% for all pharmacokinetic parameters. Reason for low power can be concluded due to sample size constraint and high intrasubject variability.

There may be different cause for failure of bioequivalence, but in current study either low sample size or problem in formulation is the possible reasons. Test formulation did not achieve the bioequivalence criterion which may be due to low absorption. Sometimes the excipients (Binders, pH adjuster, thickening agents) use in the formulation may affect the absorption of drug. Other reason could be sample size.

Cross over design use within subject comparison between treatments by separating out between subject variability components. For this reason statistician should focus on sample size because failing bioequivalence can be due to high within subject variability. A high intersubject CV indicate variation in absorption, distribution and elimination of drug across subjects. (peng chai et al)

The results of a clinical trial conducted by Gomes et al (2008) shows that treatment with olmesartan medoxomil in monotherapy or in combination showed to be very effective and safe. Tolerability of Olmesartan was also assessed by Rajiv Rana et al. (2010) in Indian patients. Results of this study showed tolerability was excellent in 92.1% of patient, with only one patient (0.1%) reported it to be poor. Similarly in current study, post dose vital signs (oral temperature, sitting blood pressure and radial pulse), clinical examination and lab assessment at end of study were found to be normal for all the subjects in all periods of the study. Except only One (01) Subject had pain in abdomen with moderate severity in period II which was resolved after treatment. The causality was possible as decide by medical supervisor. Hence it can be concluded that treatments were well tolerated by study subjects.

The results obtained in this study clearly indicate that test product A & B are not bioequivalent to the reference formulation. Hence, it is recommended that the study should be repeated with large sample size or test formulations need to be reformulated to fulfill the stated regulatory bioequivalence range of 80-125% (FDA, DCGI).