6.0 CONCLUSION

In India fixed dose combination (FDC) of drugs/medicines has drawn the attention of health service providers and the service recipients they realized the problem of wide variations in the therapeutic effectiveness of various marketed brands of oral formulations containing the same active ingredient in equal amounts.

Fixed ratio combination products are acceptable only when the dosage of each ingredient meets the requirement of regulatory guidelines (US-FDA, DCGI; EMEA), two products are generally considered to be bioequivalent if they yield comparable bioavailability when administered to the same individuals in the same dose and under similar conditions. The formulations thus deemed to be bioequivalent are therapeutically interchangeable.

In the present study we evaluated the single oral dose bioequivalence of the test formulation i.e. fixed dose combination tablet of Atorvastatin 10 mg (as Atorvastatin calcium) and Metformin HCl 500 mg ER of Ranbaxy Laboratories Limited, with Lipitor® tablets (containing Atorvastatin 10 mg as Atorvastatin calcium) of Pfizer and Glucophage® XR tablets (containing Metformin HCl 500 mg) of Bristol-Myers Squibb company, administered concurrently in healthy, adult, human male subjects under fed condition.

The clinical study was carried out in accordance with ICH Good Clinical Practices. The study protocol and the informed consent form were approved by the Jamia Hamdard Institutional Review Board. Each of the subjects was required to understand and give his consent to participate in the study by signing the informed consent form. The signed original copy was retained and a copy was given to each study subject for record. The washout period maintained between the each period was of eleven days.

Blood samples were collected within 2 minutes of the specified time as per study design. Intravenous indwelling cannula was kept in situ as long as possible, otherwise an alternative method of collecting by fresh clean vein punctures using standard disposable sterilized syringe and a needle was used. After collection, blood samples were processed under low light condition and then centrifuged as per the processing
method to separate plasma. All plasma samples were stored in suitably labeled polypropylene tubes below -50°C till analysis.

A high performance liquid chromatographic tandem mass spectrometric method for the estimation of Atorvastatin, o-Hydroxy Atorvastatin and p-Hydroxy Atorvastatin in human plasma was developed and validated using Atorvastatin D5, o-Hydroxy Atorvastatin D5 and p-Hydroxy Atorvastatin D5 as internal standards respectively and a high performance liquid chromatographic tandem mass spectrometric method for the estimation of Metformin in human plasma was developed and validated using ranitidine as internal standard. The method was linear between 0.103-200.867 ng/ml for Atorvastatin and 20.6-3219.5 ng/ml for Metformin.

The validated method of Atorvastatin and Metformin were used for the analysis of subject samples. Pharmacokinetic and statistical evaluation was done on the find concentration data obtained after analysis of samples.

The following conclusion was drawn from the study:

- Intrasubject CV was <30% for all pharmacokinetic parameters for both Atorvastatin and Metformin.
- Power was 90% throughout the study for all pharmacokinetic parameters.
- The 90% confidence intervals of C_{max} (T/R ratio) for Atorvastatin were within the 75%-133% of acceptable range. Also 90% confidence intervals of AUC_{0-t} and AUC_{0-∞} (T/R ratio) for Atorvastatin were within the 80-125% acceptable range.
- The 90% confidence intervals of C_{max}, AUC_{0-1}, AUC_{0-24} and AUC_{0-∞} (T/R ratio) for Metformin were within the 80-125% of acceptable range.
- The test and reference products were well tolerated by the study subjects.
- Hence, the test product is bioequivalent with the reference product.