CHAPTER VI

SUMMARY & CONCLUSIONS
6.0 SUMMARY AND CONCLUSIONS

Physicians have freedom to prescribe brand-name or generic drugs and health care decision makers encourage physicians to prescribe generic medications. However, medical professionals have realized the problem of wide variations in the therapeutic effectiveness for the various marketed brands of oral formulations containing the same active ingredient in equal amounts.

Several regulatory agencies (USFSDA; DCGI and EMEA) consider two products to be bioequivalent if they yield comparable bioavailability (rate and extent of absorption) 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 dose pharmacokinetics of three different marketed sustained release 100 mg diclofenac sodium tablets (Voveran SR, Nac SR, and Reactin SR) in healthy, adult, human, male subjects under fasting conditions.

The study was carried out in accordance with ICH Good Clinical Practices. The study protocol and informed consent form were approved by 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 subject for record. The washout period maintained between the each period was of four 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 veni punctures using standard disposable sterilized syringe and a needle was used. After collection, blood samples were centrifuged as per the processing method to separate plasma. All plasma samples were stored in suitably labeled polypropylene tubes at -70°C till analysis.
A validated LC-MS/MS was used for the estimation of diclofenac sodium in plasma. The method was linear between 18.75 ng/ml-2000.25 ng/ml, diclofenac concentration range with lower limit of quantification 18.75ng/ml. This method was successfully used for the analysis of diclofenac sodium concentrations in human plasma samples.

Bioequivalence was assessed by measuring the pharmacokinetic parameters namely C\text{max}, AUC\text{0-4} and AUC\text{0-\infty} for diclofenac sodium. 90% confidence interval ratios of, LSM of log transformed data for C\text{max}, AUC\text{0-4} and AUC\text{0-\infty} within 80-125% were considered to be bioequivalent.

The 90% confidence intervals for log transformed T/R ratios for C\text{max}, AUC\text{0-12}, AUC\text{0-15} and AUC\text{0-\infty} were 98.57-161.64; 90.19-126.18; 98.73-133.81 and 103.57-142.44 respectively for the test product A and 36.95-60.58; 88.2-123.14, 55.09-74.66 and 52.13-71.70 for the test product B respectively, thus all values were lying outside the specified range of 80-125%.

Dissolution performances of test products were comparable to reference product with mean similarity factor ($f_2$) which was below 50 for both the products.

The following conclusions were drawn from the study

- Both the test products were bioinequivalent to the reference product when the US FDA and DCGI criteria (confidence interval limits 80-125%) was applied. Thus, based on statistical considerations, none of the products can be substituted by the physician or the pharmacist for the reference product Voveran SR.

- Though product A fared better than product B in some BE parameters. However, both the products were not bioequivalent to product R and hence cannot be substituted for product R, with confidence. However, the clinically important consideration of avoiding multiple peaks in diclofenac plasma concentration (and hence concentration dependent ADR) by using sustained release formulations was met only by product B (Single peak) as compared to product A and product R (both showed 4 peaks). All the products maintained
product A and product R (both showed 4 peaks). No dose dumping observed with any of these formulations.

- In dissolution $f_2$ values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products. In this study product A had $f_2$ value, $>50$ and product B $<50$ against reference product R.

- Based on regulatory guidelines the order of quality of the products was as follows: $R>A>B$. However, based on clinical considerations $B>R>A$.

- Brand switching may lead to harm to patients if clinically inferior treatments are erroneously deemed equivalent to a standard approach.

- Although the generics substitution may produce considerable saving, these savings should not be offset by increase in the hospitalization, nor should the patient's therapeutic stability be compromised.

- The patient should always be informed about the switch by the physician and asked to be vigilant and immediately report in case of any changes observed in terms of adverse effects.