5.0 DISCUSSION

In the present study, the pharmacokinetic bioequivalence of three brands of lithium carbonate 400 mg extended release tablets after single dose and steady-state multiple dose in healthy, male, adult, human subjects under fasting conditions was evaluated. The reference product was Lithosun® SR 400 mg manufactured by Sun Pharmaceutical Industries Ltd., India. The test products were A: Lalithium® XR 400 mg (Manas Pharma Mfg. Ahmedabad, Gujarat, India) and B: Licab® XL 400 mg (Torrent Labs (P) Ltd. Ahmedabad, Gujarat). In-vitro dissolution study of each formulation was done as per USP 29 specifications on six tablets.

The clinical study was carried out in accordance with ICH Good Clinical Practices (1996). The study protocol and the informed consent form were approved by the Jamia Hamdard Institutional Review Board (Annexure I and III). Each of the subjects was required to read and understand the information before giving his consent to participate in the study by signing the informed consent form (Annexure II). The signed original copy was retained and one signed copy was given to the study subject for the record. The study was conducted by using an open label; balanced, randomized, cross over design in healthy, male volunteers under fasting conditions. The order of receiving the test and reference products for each subject was determined according to a SAS generated randomization schedule (Annexure IV).

The standard SOP’s of the clinical pharmacology unit (CPU) and Clinical Pharmacology and Pharmacokinetics (CPP), Ranbaxy have been adhered to in the clinical, pharmacokinetic and statistical analysis.

Bioequivalence was assessed by measuring the pharmacokinetic parameters namely $C_{\text{ssmax}}, T_{\text{ssmax}}, \text{AUC}_{0-12}$ and $C_{\text{ssmin}}, C_{\text{ssavg}}$ and % fluctuation for steady-state and $C_{\text{max}}, T_{\text{max}}$, and $\text{AUC}_{0-12}$ for single dose as laid down by the USFDA (2003) and CPMP (2002) guidelines.
The Dissolution data

The Dissolution data of Test product A (Lalithium®) and Test product B (Licab®) in dissolution medium of dilute hydrochloric acid is presented in Table A I and Table A II respectively. The dissolution rates of Product A and B in acid medium were 18% and 6% less than the minimum acceptable rate (not less than 85% at 120 minutes). Hence, both the products failed to comply with the USP 29 specifications for dilute hydrochloric acid medium. The performance of Reference Product R (Lithosun®) was above the prescribed limit (94.8%) (Table A III).

The Dissolution data of Test A (Lalithium), Test B (Licab) and Reference R (Lithosun) in water is presented in Table B I, Table B II and Table B III respectively. The dissolution rates of all the Products A and B and Reference R met the prescribed criteria (all are above 70% at 7 hours) of the USP 29 specifications.

The Reference Product R had the most desirable dissolution profile, while Test Product A had the least desirable dissolution profile. Thus, the Test Product A was not equivalent to Reference product R even in in-vitro dissolution testing. The Test Product B was marginally inferior to Reference product R.

Single Dose pharmacokinetic parameters

The T/R ratios for log transformed data for the pharmacokinetic parameters $C_{\text{max}}$, and $\text{AUC}_{0-12}$ were 82.05 and 71.68 for test product A. For the product B, the T/R ratios were 97.73 and 96.42 for $C_{\text{max}}$, and $\text{AUC}_{0-12}$ respectively.

The T/R ratios for log transformed data for the pharmacokinetic parameters $C_{\text{max}}$, and $\text{AUC}_{0-12}$ of test product A fell out of the 95-105% range. However, for test products B, the T/R ratio for log transformed data for pharmacokinetic parameters $C_{\text{max}}$, and $\text{AUC}_{0-12}$ is on the border line; but it is within the prescribed range.

The 90% confidence intervals for log transformed data for pharmacokinetic parameters $C_{\text{max}}$, and $\text{AUC}_{0-12}$ of the test product A were 74.28-90.70 and 63.77-80.58 respectively.
The 90% confidence intervals for log transformed data for pharmacokinetic parameters $C_{\text{max}}$ and $\text{AUC}_{0-12}$ of the test product B were 88.41-108.04 and 85.77-108.39 respectively.

When 90% confidence interval was applied for log-transformed data for $C_{\text{max}}$, and $\text{AUC}_{0-12}$, for both the test products, the $C_{\text{max}}$ for the both the test products fell out of the required narrow therapeutic criteria range i.e. 90-111%. The $C_{\text{max}}$ of test product B however passed the acceptance range for narrow therapeutic index drugs by US FDA and DCGI i.e. 80-125%. If the 90% confidence interval was applied of 90-111%, for log-transformed data of $C_{\text{max}}$, both the test products fell out of the required narrow therapeutic criteria range (i.e. 90-111%) of Canadian FDA.

When 90% confidence interval was applied for log-transformed data for $\text{AUC}_{0-12}$, for both the test products, The $\text{AUC}_{0-12}$ of test product B passed the acceptance range for narrow therapeutic index drugs by US FDA and DCGI i.e. 80-125% while product A fell out of the range of 80-125%.

However, when the broader US: FDA and DCGI criteria for narrow therapeutic products was applied, the test product B passed the acceptance criteria for $C_{\text{max}}$ and $\text{AUC}_{0-12}$ i.e. 80-125% at 90% CI for narrow therapeutic products while test product A fell out of the range.

Since $C_{\text{max}}$ and $\text{AUC}_{0-12}$ are considered for a potential bioequivalence or inequivalence. Both the test products fell completely outside the acceptable limits of 90-111% for the NTI drugs, but the test product B fell within the broader acceptable limits of 80-125% of US FDA and DCGI Regulatory requirements. Hence, if we apply 90% confidence interval of 90-111% range of narrow therapeutic range, both the products fell outside the desired range.

Thus, even when the comparison was done according to the broader FDA and DCGI criteria for the narrow therapeutic index drugs (i.e. $C_{\text{max}}$ and $\text{AUC}_{0-12}$ 80-125%), the
test product A failed and the test product B tended to be bioequivalent to the reference product.

The parameter $T_{\text{max}}$ was statistically evaluated using the Wilcoxon's Signed Rank Test at $\alpha = 0.05$ level of significance. A p-value of 0.250 (> 0.05) for comparison A vs. R and a p-value of 0.1563 (>0.05) for comparison B vs. R for the signed-rank statistic indicated non-significant difference between the Test product and the Reference product based on $T_{\text{max}}$ values.

A distribution-free 90% confidence interval was also constructed for median $T_{\text{max}}$ "Test – Reference" difference based on the method described in Hauschke et al 1990.

The 90% confidence interval for the median $T_{\text{max}}$ "Test – Reference" for A vs. R difference was -1.0206 to 0.1115 and the 90% confidence interval for the median $T_{\text{max}}$ "Test – Reference" for B vs. R difference was -0.8856 to -0.0233.

Thus, the non-parametric 90% confidence interval for the median $T_{\text{max}}$ "Test – Reference" difference is a narrow and acceptable confidence interval and it confirms the similarity of the rate of absorption of the two formulations.

The intra subject variability for the $C_{\text{max}}$ and $\text{AUC}_{0-12}$ was reported for log-transformed data. Overall, the intrasubject variability (expressed as %CV) for all the products was low. Intra subject variability was 13.178 and 15.405 for $C_{\text{max}}$ and $\text{AUC}_{0-12}$ respectively. (Table S-13)

P values were reported for the pharmacokinetic parameters $C_{\text{max}}$ and $\text{AUC}_{0-12}$. There was no period and sequence effect as indicated by the p values shown in Tables S-3 (p values for these effects > 0.05 from the ANOVA model). Treatment effect was shown as indicated by the p values shown in the table S-3 which is less than 0.05 from the ANOVA model.
The power of the test was high for $C_{\text{max}}$ and $AUC_{0-12}$ and was reported as 94.939% and 87.6123% respectively.

Based on the above results we can say that product B is bioequivalent to product R, as per US: FDA and DCGI 80-125% criteria for narrow therapeutic drugs, but it could be bioinequivalent, if a 90-111% criterion of Canadian FDA for narrow therapeutic drugs has been applied. While product A was bioinequivalent even by the broader FDA and DCGI criteria for narrow therapeutic drugs i.e. 80-125%.

Steady-State pharmacokinetic parameters
The T/R ratios for log transformed data for the pharmacokinetic parameters $C_{\text{ss max}}$, $AUC_{\text{ss0-12}}$ were 79.18, and 69.87 of test product A. For the product B, the T/R ratios were 93.42 and 93.77 for $C_{\text{ss max}}$, and $AUC_{\text{ss0-12}}$ respectively.

The T/R ratios for log transformed data for the other pharmacokinetic parameters viz. $C_{\text{ss min}}$, $C_{\text{ss avg}}$ and % fluctuations were 71.03; 73.79 and 120.01 respectively for the test product A. The T/R ratios for log transformed data for the other pharmacokinetic parameters viz. $C_{\text{ss min}}$, $C_{\text{ss avg}}$ and % fluctuations were 91.92; 95.70 and 99.38 respectively for the test product B.

The T/R ratios for log transformed data for all the pharmacokinetic parameters viz. $C_{\text{ss max}}$, $AUC_{\text{ss0-12}}$, $C_{\text{ss min}}$, $C_{\text{ss avg}}$ and % fluctuations of test product A fell out of the 95-105% range. However, for test products B, the T/R ratio of log transformed data for $C_{\text{ss max}}$, and $AUC_{\text{ss0-12}}$ is on the border line; while for $C_{\text{ss avg}}$ and % fluctuations it is within the prescribed range and for $C_{\text{ss min}}$ it fell out of range.

The 90% confidence intervals for log transformed data for $C_{\text{ss max}}$, $AUC_{\text{ss0-12}}$, $C_{\text{ss min}}$, $C_{\text{ss avg}}$ and % fluctuations for the test product A were 74.60-84.03; 64.92-75.21; 65.53-76.99; 69.29-78.56 and 104.09-138.35 respectively.
The 90% confidence intervals for log transformed data for $C_{\text{SS max}}$, $AUC_{SS-12}$, $C_{\text{SS min}}$, $C_{\text{SS avg}}$ and % fluctuations for the test product B were 88.02-99.15; 87.12-100.93; 84.80-99.64; 89.87-101.91 and 86.20-114.57 respectively.

When 90% confidence interval was applied for log-transformed data for $C_{\text{SS max}}$ and $AUC_{SS-12}$, for both the test products, the $C_{\text{SS max}}$ for both the test products fell out of the required criteria range i.e. 90-111%. The $C_{\text{SS max}}$ of test product B however passed the broader acceptance range for narrow therapeutic index drugs by US FDA and DCGI i.e. 80-125%. If the 90% confidence interval was applied of 90-111%, for log-transformed data of $C_{\text{SS max}}$, both the test products fell out of the required narrow therapeutic criteria range (i.e. 90-111%) of Canadian FDA.

When 90% confidence interval was applied for log-transformed data for $AUC_{SS-12}$, for both the test products, The $AUC_{SS-12}$ of test product B passed the acceptance range for narrow therapeutic index drugs by US FDA and DCGI i.e. 80-125% while product A fell out of the range of 80-125%.

Hence, when the broader US:FDA and DCGI criteria for narrow therapeutic products was applied, the test product B passed the acceptance criteria for $C_{\text{SS max}}$ and $AUC_{SS-12}$ i.e. 80-125% at 90% CI for narrow therapeutic products, while, the test product A fell out of the range.

When 90% confidence interval was applied for log-transformed data for $C_{\text{SS min}}$, $C_{\text{SS avg}}$ and % fluctuation for both the test products A and B, the CI of Test product A fell out of range of narrow therapeutic products range of 80-125% but for test product B, it fell within the range. The CI of the test product B passed the broader acceptable range of 80-125 % criteria but it fell out of narrow range of 90-111%.

Since $C_{\text{SS max}}$ and $AUC_{SS-12}$ are only considered for a potential bioequivalence or inequivalence. Both the test products fell completely outside the acceptable limits of 90-111% for the NTI drugs, but the test product B fell within the broader acceptable
limits of 80-125% of US: FDA and DCGI Regulatory guidelines. Hence, if we apply 90% confidence interval of 90-111% range of narrow therapeutic range, both the products fell outside the prescribed range.

To summarize, if the comparison was done according to the US: FDA and DCGI criteria for the narrow therapeutic index drugs (i.e. $C_{\text{ss max}}$ and $\text{AUC}_{\text{sso-t}}$: 80-125%), the test product A failed and the test product B tended to be bioequivalent to the reference product.

The parameter $T_{\text{max}}$ was statistically evaluated using the Wilcoxon's Signed Rank Test at $\alpha = 0.05$ level of significance. A p-value of 0.8105 (> 0.05) for comparison A vs. R and a p-value of 1.00 (>0.05) for comparison B vs. R for the signed-rank statistic indicated non-significant difference between the Test product and the Reference product based on $T_{\text{ss max}}$ values.

A distribution-free 90% confidence interval was also constructed for median $T_{\text{ss max}}$ "Test–Reference" difference based on the method described in Hauschke et al 1990.

The 90% confidence interval for the median $T_{\text{ss max}}$ "Test – Reference" for A vs. R difference was -0.3795 to 0.5613 and the 90% confidence interval for the median $T_{\text{ss max}}$ "Test–Reference" for B vs. R difference was -0.4887 to 0.4887.

Thus, the non-parametric 90% confidence interval for the median $T_{\text{ss max}}$ "Test–Reference" difference was narrow and acceptable confidence interval and it confirmed the similarity of the rate of absorption of the active ingredient from the two formulations.

The intra subject variability for the pharmacokinetic parameters $C_{\text{ss max}}$, $\text{AUC}_{\text{sso-12}}$, $C_{\text{ss min}}$, and $C_{\text{ss avg}}$ was low. However, for the % fluctuations it was high.

P values were reported for the pharmacokinetic $C_{\text{ss max}}$, $\text{AUC}_{\text{sso-12}}$, $C_{\text{ss min}}$, $C_{\text{ss avg}}$ and % fluctuations. There were no period and sequence effects as indicated by the p
values shown in Tables S-3) (p values for these effects > 0.05 from the ANOVA model). Treatment effect was shown as indicated by the p values shown in the table S-3 which is less than 0.05 from the ANOVA model.

The power of the test was high for $C_{\text{ss max}}$, $AUC_{0-12}$, $C_{\text{ss min}}$ and $C_{\text{ss avg}}$ and was reported as 99.948%, 99.577%, 99.041% and 99.90% respectively. The power of test was; however, low for % fluctuations; about 72.38%.

Based on the above results we can say that product B is bioequivalent to product R, as per US: FDA and DCGI criteria for narrow therapeutic drugs, but it could be bioinequivalent, if a 90-111% criterion (Canadian FDA) for narrow therapeutic drugs has been applied. While product A was bioinequivalent even at broader US: FDA and DCGI criteria for narrow therapeutic drugs i.e. 80-125%.

The rising cost of health care has compelled health agencies and regulatory bodies to devise strategies to decrease costs without compromising the health care services. One such method is to encourage use of generic drugs. While it can reduce costs of health budget by 50%, it is critical that it is not achieved on the expense of quality of health care (Spino M et al, 2000).

In the last 30 years the prescription of generic drugs dispensed in US has increased to 40-50% of all prescriptions (Covington TR, 1992; Shah HK, 1992). Developing countries do not have a fool proof means of checking the quality of generics which result in substandard products. These potentially substandard formulations raise questions concerning suboptimal clinical response or emergence of side-effects on switching from one brand to another. A generic copy of reference drug must contain identical amounts of the same active ingredients in the same dose formulation and route of administration, as well as meet standards for purity, quality and identity. Some inactive ingredients such as binders and fillers are allowed to differ, but must occur in the similar ratio to the active compound as that observed in the brand name drug (CDER, 1999). Different manufactures use various methods to formulate these products so many of these marketed formulations may differ in the rate and extent of
absorption (Hendels et al, 1984; Weinberber et al, 1978). A study of biopharmaceutics gives ample evidence that the method of manufacture and the final formulation of drug can markedly affect the bioavailability.

The dissolution procedures specified by the United States Pharmacopoeia (USP) can be used to test batch-to-batch uniformity, to detect manufacturing or process variation that might influence the bioavailability and to document formulation bioequivalence (CDER, 2003). Product A did not meet the In-vitro USP dissolution test requirements in acid medium, and it was also bioinequivalent to the reference product R in In-vivo bioequivalence testing. The use of in-vitro dissolution test, as a predictor of In-vivo performance has been specified to document batch to batch or lot to lot quality of a drug product (CDER, 2003). It appears that the manufacturer of product A is not conducting even the In-vitro dissolution testing of each and every batch marketed by it, to ensure continuous drug product quality and performance, since it is not a specified test for lithium formulations in the Indian Pharmacopoeia.

In 1986, the Pharmaceutical Manufacturers Association (PMA) proposed that the use of a single regulatory acceptance range for all drugs should be replaced by an individualized drug by drug approach, in which the regulatory authorities would determine the acceptance limits at the time of the branded drug's patent expiry (Pidgen A et al, 1996). However, to-date the regulators have not adopted this proposal. The consensus is that the bioequivalence testing should be preceded by an assessment of the therapeutic window and an estimate of intra-subject and inter-subject variability (Meredith P, 2003).

The bioequivalence requirements for approval of generic products differ among various countries. The use of a single regulatory limit by US: FDA has been criticized with respect to the narrow therapeutic index drugs, and some clinicians propose that more rigid bioequivalence guidelines are needed for these specific drugs (Banahan BF III and Kolassa EM, 1997).
While case reports continue to surface questioning the therapeutic equivalence of selected generic products, the FDA firmly believes that any differences that could exist are no greater than would be expected if one lot of the innovator’s product was substituted for another. Nevertheless, some investigators believe that different approaches may be needed to ensure “switchability” among multisource products, such as testing NTI drugs under clinical conditions in the target population or narrowing the confidence interval allowed for average bioequivalence, or by applying individual bioequivalence criteria. Tighter acceptance criteria or narrower confidence intervals have been proposed for NTIs and are required by some drug regulatory agencies (e.g., Canada and EU). However, the FDA believes that the present requirements to prove bioequivalence are rigorous enough to prevent the possibility that dosage forms meeting regulatory criteria could lead to therapeutic problems, even for NTI drugs (AMA Annual Report, 2002).

Clinical practice has revealed that risks involved in the switch from brand to generic drugs are particularly marked in certain situations like (stroke, epilepsy, bipolar disorders, immunosuppressive therapy in transplantation and depression) any change in the safety and efficacy compared with the original drug may result in the serious or fatal complications. The risks are also increased when the original drug has a narrow therapeutic index, non-linear kinetics or poor solubility in water. The use of different type of the salt may have unforeseen consequences. Patients may also be at risk if the legal environment inhibits the physicians control and vigilance and mandates a compulsory switching by the pharmacists. (Meredith P, 2003).

Lithium carbonate is a poorly soluble in water and it is a narrow therapeutic index drug so it is a potentially dangerous drug for substitution.

Therefore, generic substitutions especially of NTI drugs in the diseases like epilepsy, bipolar disorder etc. should be allowed only if the patient safety and efficacy is suitably monitored. Some of the suggested measures are;
• The blood levels are constantly monitored by Therapeutic drug monitoring especially when there is a switch made from brand to generic product and the medication doses are be adjusted accordingly

• Specific information about the antipsychotic drug is made available to the physician especially serum levels, Area under the curve, dissolution profile, Time to maximum plasma concentrations and reported complications

• Pharmacist should inform the patient and also the physician whenever he is switching the formulations.

• The patient and his/her relatives 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 or increase in the frequency of disease episodes.

A program of action should be put into place to ensure that such switches are safe and less problematic than is now the case. This would necessitate the (i) conduct of BE studies with adequate samples of specific patients groups (age, sex and disease) as well as healthy volunteers and (ii) Double blind studies comparing the safety and efficacy of the generic with the brand name drug, and economic studies of actual savings produced by a switch to generic drug (Borgherini G, 2003).

Health care staff, patients and family members would have to be provided with adequate information on the risks and limitations associated with the therapeutic switch. An effective pharmacovigilance network would need to be created to perform periodic pharmacoepidemiologic surveys of doctors and specialists to elicit any observed differences between the brand-name and the generic drugs (Borgherini G, 2003).

Although substituting a generic in bipolar disorders, epilepsy etc. may produce considerable savings given the chronic nature of the disease, but these savings should not be offset by increased hospitalization cost by therapeutic failure, nor should patient's therapeutic stability be compromised.
Limitations of the study and future studies proposed

This bioequivalence study was conducted at the single dose as well as steady state levels. Steady-state was not reached even after 11 doses of lithium carbonate with all the three formulations tested. In future studies a longer duration of treatment needs to be used.

Number of subjects taken in the study was 15 due to limitation of time and lack of funds and hence in future more number of subjects should be taken in order to enhance the power of the study.

Additionally, more brands should be compared which was not possible here because of constraint of time and research funds in this thesis project.