CHAPTER 5.

DISCUSSION
5.0 DISCUSSION

The capacity of India to produce and export generic medicines has been vital to public health, particularly in developing countries but also for consumers in rich countries such as the US. Generic competition slashes the price of medicines like first-line anti-retrovirals went from $10,000 per patient per year down to less than $140 as a result of generic competition, benefiting millions of poor HIV/AIDS patients in the developing world. Affordable, high-quality generics from India are critical to UN and bilateral treatment programs. Half the essential medicines distributed by UNICEF in developing countries come from India; 70% of treatment for HIV/AIDS patients in 87 countries provided by UNICEF, the International Dispensary Association and the Global Fund comes from India and US President HIV/AIDS initiative sources 70% of its anti-retroviral drugs from India. (MSF 2007, UNICEF annual report 2005)

Low-cost manufacturing techniques and generic competition in India have also drastically reduced the prices of thousands of other medicines. Medicines that can prevent cardiovascular disease, treat diabetes and alleviate mental illness are available at prices that are 90%-95% the cost of a brand name version. (Hobbs J, 2007)

Many developing countries like India do not have an effective means of monitoring the quality of generic drug products in the market which results in wide distribution of substandard and/or counterfeit drug products. (Patel, 2005).

Almost a third of the WHO member countries have poor means of controlling substandard medication. (Carpenter 2006). The WHO estimates that up to 10% of the worlds pharmaceutical trade (25% in developing countries) consists of fakes (Pincock, 2003). As per the US FDA, of all drugs consumed in poor countries, 25% are thought to be counterfeit or substandard (Rudolf 2004). Medicine sellers often exhibit lack of concern about expiration dates and storage conditions, especially in poor settings and in the absence of national control, and this can increase the spread of substandard antimicrobials (Murtarda et. al. 1994; Prazuck et. al 2002). Manufacture of generic versions of patented drugs for humanitarian reasons may also be abused in developing countries (Bouchie, 2003 ; Newton et.al., 2006) The issue of monitoring the quality of generic drugs is limited not only to countries like India but also in the most developed nations (Gibaldi, 2005). Individuals and a few state and local governments are turning to Internet and foreign pharmacies, particularly Canadian pharmacies to find less costly medications. However, these internet pharmacies...
increasingly buy from foreign sources themselves to meet the demands from America (Spake, 2004).

In India, several formulations of a drug are available in the market and there is a significant difference in cost among these products from innovator brands. The definition of a new drug as per the Drugs and Cosmetics act of India is exploited by manufacturing firms to market products without bioequivalence studies, which give rise to question for the switchability and interchangeability of generic and brand name drugs.

The present study was designed to determine the interchangeability of different brand of metformin extended release formulations in normal healthy subject by using pharmacokinetic end points.

The objectives of the present study therefore were:

- To compare the single-dose oral bioavailability of two low price brands of metformin 500mg extended release tablets with more expensive brand available in the Indian market in healthy, human subjects under fed conditions.

| Reference (R) | Cetapin XR extended release Tablets (Aventis Pharma Ltd.) |
| Test (A)      | Glycomet SR 500mg extended release tablets (USV Pharma Ltd.) |
| Test (B)      | Bigomet SR extended release tablets (Otsira Genetica Ltd.) |

- To check whether economical low price brands of metformin could be substituted safely and successfully for costlier one.

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 II). Each of the subjects 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 III).

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.

5.1 Adverse Events
The three formulations of Metformin extended release administered in healthy volunteers had an excellent tolerability with no adverse events reported. Only one subject dropped out from the study before dosing in period I citing personal reasons. The remaining 17 enrolled subjects completed the study according to protocol.

Similar single dose pharmacokinetic studies with 500 mg extended release metformin tablets reported mild adverse events which did not lead to discontinuation of therapy. Karttunen et. al. (1983) reported mild abdominal pain and Timmins et. al. (2005) reported Gastrointestinal, hematopoietic, musculoskeletal and genitourinary involvement in adverse events. However the study by Timmins also had a steady state arm and therefore the larger number of adverse events.

5.2 Bionalytical Method Development and Validation
Several methods have been developed for the determination of metformin in biological samples. Most of them are based on either HPLC or liquid chromatography tandem mass spectrometry (LC/MS/MS) method (Heinig et. al., 2004; Tahara et. al., 2006).

In developing an analytical method for pharmacokinetic studies, in addition to the sensitivity, reproducibility and suitability, time and labour-saving factors must be considered. In a bioequivalence study a large number of samples need to be examined. In general, sampling and sample preparation steps account for over 80 % of the whole analysis time, thus development of sample preparation plays a very important role in pharmaceutical analysis. An ideal extraction method should be rapid, simple, inexpensive, and give reproducible and high recoveries without the possibility of degradation of the analytes (Fu et al, 2005).
Therefore a simple, rapid, economical, isocratic, LCMS method employing a liquid-liquid extraction followed by MS detection for the estimation of metformin in human plasma was developed and validated according to FDA guidelines (CDER, 2001). For validation of analytical method, selectivity, accuracy and precision, linearity, recovery (drug and internal standard), and stability (freeze thaw, bench top, in-injector) exercises were performed.

This developed liquid extraction based LCMS method was selective for analysis of metformin in plasma with deuterated metformin as an internal standard. The use of this method offers advantage in terms of per sample preparation cost and time in comparison to solid phase extraction. The validity, limit of quantification and linearity range of method makes it an acceptable method for clinical studies in patients and in bioequivalence studies.

For plasma sample processing, liquid-liquid extraction procedure was accomplished by using acetone. A positive ion spray LCMS was used for the analysis of the samples. Calibration curves were plotted against area ratio (drug/IS) Vs concentration ratio and was found to be linear from 38.6-2033.4 ng/ml for metformin. Between batch accuracy and precision (three batches) was 95.4-106.3 % and 97.1-104.9 % respectively. Mean recovery of metformin and metformin-D6 (internal standard) in plasma were 49.4 % and 52.7 % respectively. Bench top stability for 6 hours at bench was found to be 94.5-103.4 %. Freeze thaw and in-injector were 102.8% 103.8%, 99.9-106.9 % and 96.1-98.2 % respectively.

5.3 Pharmacokinetic Parameters

Bioequivalence was assessed by measuring the pharmacokinetic parameters namely C<sub>max</sub>, T<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> for single dose as laid down by the CDER (2003) guideline.

The A/R ratios for least squared mean log transformed data for the pharmacokinetic parameters C<sub>max</sub> (ng/ml), AUC<sub>0-t</sub> (ng.hr/ml) and AUC<sub>0-∞</sub> (ng.hr/ml) for test product A were 90.12, 93.89 and 94.12 respectively. This indicates that pharmacokinetic parameters for test product ‘A’ resembled that of the reference product ‘R’, and ideally these values should lie between 80-120%.

The 90 % confidence intervals for the ratios of the log transformed data for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> for the test product A vs. reference R (A/R) were 82.11-98.91, 86.29-102.17 and 86.34-102.59 respectively. This indicates that AUC<sub>0-t</sub> and AUC<sub>0-∞</sub> of test product A vs. reference R (A/R) ratio were within the stated regulatory bioequivalence range of 80-125.
(FDA, DCGI) in the fed state. Therefore, the test product A (Glycomet SR) is bioequivalent to reference product R (Cetapin XR) under fed conditions.

The B/R ratios for log transformed data for the pharmacokinetic parameters $C_{max}$ (ng/ml), $AUC_{0-1}$ (ng.hr/ml) and $AUC_{0-\infty}$ (ng.hr/ml) for test product B were 114.58, 103.13 and 101.22 respectively. Although pharmacokinetic parameters of $AUC_{0-1}$ (ng.hr/ml) and $AUC_{0-\infty}$ (ng.hr/ml) for test product 'B' resembled that of the reference product 'R', however the $C_{max}$ of the ratios did not lie in this range.

The 90% confidence intervals (CI) for log transformed data for $C_{max}$, $AUC_{0-24}$ and $AUC_{0-\infty}$ for the test product B Vs reference R (B/R) were 104.39-125.76, 94.78-112.22 and 92.85-110.33 respectively. The CI values of $C_{max}$ do not fall under the required regulatory bioequivalence range of 80-125 (FDA, DCGI). Therefore, it can be concluded that test product B (Bigomet SR) does not pass the bioequivalence criteria to reference product R (Cetapin XR) under fed conditions.

The median $T_{max}$ for the formulations A, B and R were 6hrs, 5hrs and 5.5 hrs respectively. The parameter $T_{max}$ was statistically evaluated using the Wilcoxon's Signed Rank Test at $\alpha = 0.05$ level of significance and a distribution-free 90% confidence interval was also constructed for median $T_{max}$ "Test – Reference" difference based on the method described in Hauschke et al (1990).

For comparison A vs. R, a p-value of 0.3932 (> 0.05) for the signed-rank statistic indicated no significant difference between the Test product (A) and the Reference product (R) based on $T_{max}$ values. The 90% confidence interval for the median $T_{max}$ "Test – Reference" difference was -0.5 to 1.00.

For comparison B vs. R, a p-value of 0.5001 (> 0.05) for the signed-rank statistic indicated no significant difference between the Test product (B) and the Reference product (R) based on $T_{max}$ values. The 90% confidence interval for the median $T_{max}$ "Test – Reference" difference was -1.5 to 1.00.

Based on the Wilcoxon signed rank statistic (which suggested a non-significant difference between A vs. R and B vs. R) and the narrow and acceptable 90% confidence interval for the median $T_{max}$ "Test – Reference" difference confirms the similarity in $T_{max}$ for the two formulations.
AUC_{0-t}/AUC_{0-inf} (%) for all products were more than 80 % emphasizing that the duration for sample collection was appropriate which covers more than 80 % of complete drug profile.

The intrasubject variability for the C_{max}, AUC_{0-t} and AUC_{0-inf} was reported for log-transformed data. Overall, the intrasubject variability (expressed as % CV) for all the products was 16.1, 14.6 and 14.9 for C_{max}, AUC_{0-t} and AUC_{0-inf} respectively.

The pharmacokinetic parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}) were analyzed using an ANOVA model with the main effects of sequence, period and formulations as fixed effects and subjects nested within sequence as random effect.

A separate ANOVA model was used to analyze each of the parameters. All the effects were tested at the 0.05 level of significance against the residual error (mean square error) from the ANOVA model as the error term. The sequence effect was significant for C_{max} however it is not significant for AUC_{0-t} and AUC_{0-inf}.

Generally for a crossover study, the presence of sequential effect is acceptable if some of the following criteria are observed

I) it is a single dose study;

II) the study it involves only healthy subjects;

III) the drug is not an endogenous substance;

IV) an adequate washout period was established and the pre-dosage samples do not present any level of detectable drug in all the subjects;

V) the study meets all the scientific and statistical criteria (e.g. protocol, validation, concentration data, statistical analysis, confidence interval).

The present study was conducted as a 3-way crossover single dose study on healthy volunteers. Further metformin is also not an endogenous substance. As per the literature the reported half-life of metformin is 4-7 hours. Based on this an adequate washout of 7 days was provided between the two periods so as to remove the effect of period I dosing completely. This is further reconfirmed as no concentration was observed in pre-dose sample during period II and period III of the study. Hence we assume the significant period effect observed for C_{max} should not have any impact of study outcome.
In this study a significant treatment effect was also seen in \( C_{\text{max}} \). In a Bioequivalence study, approach adopted is based on rejecting the null-hypothesis of Non-Bioequivalence by means of interval estimates (90\% Confidence Interval - Two one-sided Test) in which we test whether the Test/Reference ratio (In-transformed data) lie within the bio-equivalence range or not.

\[
\text{H}_0: \ln \frac{\mu_T}{\mu_R} \leq \ln \theta_L \quad \text{or} \quad \ln \frac{\mu_T}{\mu_R} \geq \ln \theta_U
\]

against

\[
\text{H}_1: \ln \theta_L < \ln \frac{\mu_T}{\mu_R} < \ln \theta_U
\]

Where

\((\theta_L, \theta_U) = \text{Bioequivalence Range} . \)

\( \mu_T, \mu_R = \text{Expected mean values of Test and Reference formulations.} \)

Whereas, Treatment effect in ANOVA refers to testing of the null hypothesis that the two formulations under consideration are identical, i.e. their ratio is 1.

\[
\text{H}_0: \mu_T = \mu_R \quad \text{against} \quad \text{H}_1: \mu_T \neq \mu_R
\]

Hence, the statistical inference from a p-value obtained from ANOVA (i.e. aiming at the difference between the two formulations) is completely different from the statistical inference from the 90\% confidence interval in bioequivalence testing and therefore the treatment effect detected by ANOVA would not have an impact on the final bioequivalence conclusions.

The significance of p-value obtained from ANOVA in Bioequivalence evaluation is not a true reflection of Bioequivalence conclusions and it is the 90\% confidence interval calculated based on Two one-sided Test that reflects the equivalence of the two products tested.

A significant treatment effect can also occur when the confidence interval does not cross unity and could happen in a situation where sample size relative to sample variance provides "too much power"; resulting in a trivial difference (too small to be important clinically) being statistically significant (Lockyer et. al. 2005).

Power of the test for \( C_{\text{max}}, \text{AUC}_{0-4} \) and \( \text{AUC}_{0-\infty} \) were found to be 97.22 \%, 98.80 \% and 98.55 \% respectively. Hence the study was adequately powered to detect any significant differences in the pharmacokinetics parameters within 90\% CI.
Based on the above results we can assume that product A is bioequivalent to product R, as per US: FDA and DCGI 80-125 % criteria under fed conditions, while product B is not bioequivalent by the FDA and DCGI bioequivalence criteria under fed conditions.

The $C_{\text{max}}$ with extended release tablets of Glucophage in the Caucasian population has been reported to be 600ng/ml (Glucophage XR USPI, 2006) while Timmins et al has reported a $C_{\text{max}}$ of 645ng/ml representing an 8% increase in $C_{\text{max}}$. In the present study using the reference extended release formulation (Cetapin XR), $C_{\text{max}}$ was higher by 31% of that reported by Glucophage 500mg XR tablets and 22% higher as reported by Timmins et al. (2005).

The reason for the higher plasma concentrations of metformin in Indian subjects may be attributed to genetic variations in the Organic cationic transporter OCT 1 and 2. Shu et al.(2007) reported a 15% and 20% increase in $C_{\text{max}}$ and AUC respectively following single dose administration of Metformin 850mg in OCT1 variant subjects. Song et al.(2008) reported $C_{\text{max}}$ values for metformin which were 1.62-fold higher in variant OCT 2 Korean subjects.

Metformin is not a narrow therapeutic index drug, therefore the increased $C_{\text{max}}$ would not result in a significant increase in pharmacodynamic effect, but may result in an increase of concentration dependent adverse effects (Lalau et al.1995).

As a measure of relative bioavailability, $C_{\text{max}}$ is inherently more variable than AUC. The CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP, 1998) goes on to state that the wider interval for 90% CIs of $C_{\text{max}}$ must be prospectively defined e.g. 0.75-1.33 and justified addressing in particular any safety or efficacy concerns for patients switched between formulations.

$C_{\text{max}}$ variability is expected to be especially high in case of drugs such as metformin that demonstrate decreased absorption with increasing doses.

The important consideration in this case would be: “Are 90% CIs of $C_{\text{max}}$ falling marginally outside the conventional 80 – 125% limits, but within 75 – 133% limits, expected to have any bearing on the safety or efficacy of the formulation B?”

The use of wider 90%CIs of the $C_{\text{max}}$ of Metformin extended release formulation will have no implications for safety and efficacy of the formulation B.
The efficacy of drugs in general is not related to the $C_{\text{max}}$. $C_{\text{max}}$ is a short-lived phenomenon; concentrations at and around the $C_{\text{max}}$ are maintained only briefly and as such the $C_{\text{max}}$ is not expected to have an impact on drug efficacy and treatment outcome.

There are several clinical situations where the $C_{\text{max}}$ of Metformin extended release formulation is reported to be either higher or lower, but without an impact on safety or efficacy of the drug.

Clinical situation where a lower $C_{\text{max}}$ of Metformin extended release formulation is documented to have no impact on the efficacy:

Following a single oral dose of Metformin XR tablet, $C_{\text{max}}$ is achieved with a median value of 7 hours and a range of 4 hours to 8 hours. Peak plasma levels ($C_{\text{max}}$) are approximately 20% lower compared to the same dose of Metformin immediate release tablet, however, the extent of absorption (as measured by AUC) is similar to Metformin immediate release tablet. In a randomized trial, patients currently treated with Metformin immediate release tablet were switched to Metformin XR tablet. Results of this trial suggest that patients receiving Metformin immediate release tablet treatment may be safely switched to Metformin XR tablet once daily at the same total daily dose, up to 2000 mg once daily (GLUCOPHAGE XR US Prescribing Information of, 2006).

Although the $C_{\text{max}}$ levels of Metformin XR tablet are 20% lower in comparison to the Metformin immediate release tablet still patients could be switched from Metformin immediate release tablet to Metformin XR tablet which means slightly lower $C_{\text{max}}$ values won’t have much impact on the efficacy and safety of Metformin XR tablet when administered to patients.

II. Clinical situations where a higher $C_{\text{max}}$ of Metformin extended release formulation is documented to have no impact on the safety:

1. In a single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin $C_{\text{max}}$ and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. $T_{\text{max}}$ and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on Nifedipine (GLUCOPHAGE XR US Prescribing Information, 2006).
2. In a single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood $C_{\text{max}}$ by 22% and blood AUC by 15%, without any significant change in metformin renal clearance (GLUCOPHAGE XR US Prescribing Information, 2006).

Neither the US prescribing information nor the UK SPC of Metformin extended release tablet recommend any change in dosage when given concomitantly with nifedipine or furosemide; implying that the extent of increase in the $C_{\text{max}}$ and AUC associated with these interactions is considered to be within the well tolerated limits.

Metformin extended release tablet is not a 'narrow therapeutic ratio' or a 'critical dose drug'. Drug products are identified as having a Narrow Therapeutic Ratio if (a) there is less than 2-fold difference between median lethal dose and median effective dose; or (b) there is less than 2-fold difference between minimum toxic concentrations and minimum effective concentrations in blood; and safe and effective use of the drug product requires careful titration and patient monitoring.

Critical Dose drugs are those drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures, and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening events.

The minimum recommended therapeutic dose for Metformin extended release tablet is 500 mg once daily; and the maximum permitted dose is 2000 mg once daily. Thus, the maximum recommended dose is 4 times the minimum recommended dose. Studies using single oral doses of Metformin 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

There being a 4 fold difference between the minimum and maximum recommended doses; and less than proportionate increase in plasma concentrations of metformin; the minimum toxic concentrations can be safely considered to be more than 4 times the minimum effective concentrations. Thus, metformin cannot be identified as having a "Narrow Therapeutic Ratio" or being a "Critical Dose drug". As such it would be acceptable to consider wider limits for 90% CIs of a drug that does not fit the definition of narrow therapeutic ratio or critical dose drug.
An analysis of the LSM ratios of the pharmacokinetic parameters of product B/ Product A were 127.14, 109.84 and 107.54 respectively for $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ (table 5.1). The upper limit of the CI for $C_{\text{max}}$ is 139.55 which goes on to show that under fed conditions, product B is not interchangeable with product A, even by the CPMP criterion of wider (75-133%) of 90% CI.

Table 5.1: Summary statistics of different pharmacokinetic parameters of single dose extended release metformin for product B vs. product A (B/A) in healthy adult human male subjects ($n=17$)(Calculated from the Geometric means of the log transformed data of individual subjects represented in Table 4.18 and 4.19).

<table>
<thead>
<tr>
<th>Product/Statistics</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$AUC_{0-t}$ (ng.h/mL)</th>
<th>$AUC_{0-\infty}$ (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>710.292</td>
<td>7402.5776</td>
<td>7847.4146</td>
</tr>
<tr>
<td>CV(%)</td>
<td>62.7</td>
<td>62.3</td>
<td>62.6</td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Product B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>899.248</td>
<td>8132.1389</td>
<td>8440.8212</td>
</tr>
<tr>
<td>CV(%)</td>
<td>61.5</td>
<td>62.4</td>
<td>61.5</td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Least square mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>704.635</td>
<td>7379.3758</td>
<td>7823.1993</td>
</tr>
<tr>
<td>B</td>
<td>895.889</td>
<td>8105.4148</td>
<td>8413.4345</td>
</tr>
<tr>
<td>Ratio of least squares mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B/A(%)</td>
<td>127.14</td>
<td>109.84</td>
<td>107.54</td>
</tr>
<tr>
<td>90% Confidence Intervals (B/A)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Limit:</td>
<td>115.84</td>
<td>100.94</td>
<td>98.66</td>
</tr>
<tr>
<td>Upper Limit:</td>
<td>139.55*</td>
<td>119.52</td>
<td>117.23</td>
</tr>
<tr>
<td>p-value[ANOVA]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Power (%)</td>
<td>97.22</td>
<td>98.80</td>
<td>98.55</td>
</tr>
<tr>
<td>Intra-subject CV(%)</td>
<td>16.1</td>
<td>14.6</td>
<td>14.9</td>
</tr>
</tbody>
</table>
5.4 Dissolution data

The dissolution procedures specified by the United States Pharmacopoeia (USP, 2007) are generally 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). The use of in-vitro dissolution test, as a predictor of in-vivo performance has been specified to document batch to batch or a lot to lot quality of a drug product (CDER, 2003). Metformin is readily soluble in water and possess low permeability thereby belongs to BCS class III classification. The rate limiting step for this is in-vivo dissolution of drug at its site of absorption.

In vitro dissolution test was performed to compare the release profile of the test products A & B with that of the reference product R using the method specified in USP. Phosphate buffer at pH 6.8 ± 0.1 was used as dissolution media and absorbance was measured by UV Spectrophotometer at 223 nm after sampling at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 15 hrs. Both test products A as well as B showed a comparable dissolution profile with that of the reference product as shown in Fig. 4.6.

A simple model independent approach was also used to compare dissolution profiles with the help of a difference factor \( f_1 \) and a similarity factor \( f_2 \) (Moore et. al., 1996). Using the mean dissolution values from both curves at each time interval, difference factor \( f_1 \) and similarity factor \( f_2 \) were calculated for the product A & B as shown in the Table 4.32 & 4.33 respectively. The mean similarity factor \( f_2 \) and mean difference factor \( f_1 \) were 95.96 & 82.54 and 13.38 & 5.59 for the product A & B respectively. These results indicate that both similarity factor \( f_2 \) and difference factor \( f_1 \) are found to be in accepted range and therefore similar performance of tests and reference products. For curves to be considered similar, \( f_1 \) values should be close to 0, and \( f_2 \) values should be close to 100. Generally, \( f_1 \) values up to 15 (0-15) and \( f_2 \) values greater than 50 (50-100) ensures sameness or equivalence of the two curves and, thus, of the performance of the test and reference products. Based on in-vitro dissolution data we can say that Test A and B are equivalent to Reference R.

These results clearly indicate that product A is bioequivalent to product R based on both in vivo pharmacokinetics results and in vitro dissolution data. So it can be interchangeable with costly reference product R and can save 30% in prescription brand cost. However product B is not bioequivalent to product R as upper limit of 90 % confidence intervals for log
transformed data for \( C_{\text{max}} \) was 125.76\%, which lies outside the range of specified US: FDA and DCGI 80-125 criteria. But in vitro dissolution data support the same release profile of product B with product R. Although product B is not bioequivalent as it failed by marginal values at the upper side in 90\% confidence interval, in spite of having a good rin-vitro equivalence.

The subject of generic substitution of branded products is still controversial despite the introduction of more stringent requirements for bioequivalence. Much of the current debate focuses on perceived problems with the design of bioequivalence studies, and a number of important issues have been identified.

The FDA maintains that the criteria used to ensure bioequivalence among multisource products do not allow for 20\% difference in bioavailability between products. Rather, these parameters represent the statistical universe in which measures of variance must reside. The FDA requires that 90\% confidence intervals be placed on the ratio of test vs control products and that this interval is within 80\% to 125\% of the mean. To meet the second condition, the difference in average \( C_{\text{max}} \) and AUC of the 2 products is usually very small. Thus, the average differences in AUC values between a brand-name product and a generic product are typically 5\% or less (Gibaldi, 2005).

Additionally, the same criteria for bioequivalence are applied to brand name products when they undergo a formulation change, which often occurs prior to marketing. These reformulated brand name products also are never tested in a clinical population. (AMA annual featured report—Generic Drugs, 2002)

It is assumed that bioequivalence in healthy volunteers will equate to both bioequivalence and comparable efficacy and tolerability in patient populations, but the validity of this assumption is questionable. This issue is particularly relevant to patient populations in which drug pharmacokinetic properties are known to differ between healthy young subjects and elderly patients in whom a number of factors, including physiologic changes associated with age and polypharmacy, give rise to substantial differences in pharmacokinetic properties compared with normal and healthy subjects (Gerbino et al., 1993).

The use of single doses is also a point of contention. Most drugs require multiple dosing to achieve steady state, and the plasma concentrations achieved after such a dosing regimen can be greater than those seen after only a single dose.
Therefore, the design of current bioequivalence studies do not accurately reproduce the clinical situation. This is of particular relevance in the testing of bioequivalence of enteric-coated products, in which multiple doses are thought to trigger changes in the gastric environment that lead to more pronounced differences in the bioavailability of two formulations. In these products, multiple-dose studies may be more discriminating (Meredith, 2003).

In conclusion, brand switching may reduce upfront costs but a program of action should be put into place to ensure that such switches are safe and less problematic in the long term cost benefit for the patient. To start with this would necessitate the conduct of BE studies with adequate samples of specific patients groups (age, sex, disease) as well as healthy volunteers comparing the generic with the brand name drug, and pharmacoeconomic studies of actual savings produced by a switch to generic drug. (Borgherini, 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, 2003)

As can be seen from the results of the in-vitro results of this study, a dissolution test is not a very good predictor of the In-vivo profile of the formulations.

5.5 Limitations of the study

- Absence of fasted arms for the direct comparison of fed and fasted states of the Pharmacokinetic parameters.

- A multiple dose steady-state pharmacokinetics would have been more informative to determine the interchangeability of products as metformin requires multiple dosing over an extended period of time.

- Studies in higher strengths of metformin extended release formulations to corroborate the higher plasma concentrations observed.