**ABSTRACT**

Doxazosin is used for treating symptoms of benign prostatic hyperplasia (BPH). Besides, it is also prescribed for patients with mild to moderate essential hypertension. The object of the current study was to assess the linearity in the pharmacokinetics of doxazosin after administration of doxazosin as a single dose tablet containing 2, 4 and 8 mg doxazosin mesylate. Thirty Iraqi healthy male adult subjects were given 2, 4 and 8 mg doxazosin mesylate tablet in a randomized, cross-over, open-label, fasting, three-period, three-sequence design separated by one week wash out interval between dosing. Serial blood samples were obtained from each subject before drug intake (zero time) and then at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36, 48, 60, and eventually at 72 hours after dosing. The pharmacokinetic parameters $C_{\text{max}}$, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow \infty}$, $T_{\text{max}}$ and $T_{\text{half}}$ were determined from plasma concentration-time data of the drug by non-compartmental analysis. Statistical analysis of doxazosin pharmacokinetic parameters obtained after administration of the investigated dose ranges 2-8 mg demonstrated linear pharmacokinetics.

**INTRODUCTION**

Doxazosin mesylate is a quinazoline derivative, its chemical name is 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine methanesulfonate, its molecular formula is $C_{23}H_{25}N_5O_5$, $CH_4O_3S$, and its molecular weight is 547.6. Doxazosin products are available as tablets containing doxazosin mesylate equivalent to 1, 2, 4 and 8 mg of doxazosin as the free base (Cardura®, 2016).

Benign prostatic hyperplasia (BPH) is a progressive disease that is often associated with uncomfortable lower urinary tract symptoms such as urgency, frequent urination, nocturia, sensation of incomplete bladder emptying, decreased and intermittent force of the stream. This disease is one of the most common urological problems that occurs in over 50% of men approaching the age of sixty years. Therefore, patients suffering from BPH symptoms report a considerable reduction in the quality of life and cause cost healthcare agencies millions of dollars for the treatment of BPH and the subsequent progressive worsening, including bladder outlet obstruction, urinary obstruction and sexual dysfunction (Bechis et al., 2014).

Five alpha-blockers are currently used for the treatment of BPH, including alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin. These drugs are widely and commonly used worldwide since...
they are recommended as the first-line treatment for BPH (Shrivastava, 2014; Shrivastava and Gupta, 2012).

Doxazosin (Alpha1-adrenoceptor antagonist) exhibits a significant effect in reducing lower urinary tract symptoms and BHP by improving the symptoms and urinary flow rate. It has a rapid onset of effect with improvement in peak flow and symptoms of BPH observed within 1-2 weeks after therapy (Roehrborn and Schwinn, 2004; Wilt and Macdonald, 2006). Doxazosin is also used for treating mild to moderate essential hypertension (Wytretowicz et al., 2008).

Doxazosin can be also indicated in the treatment of distal ureteral calculi since recent studies indicated that doxazosin administration caused a significant increase in stone expulsion rate and a decrease in expulsion time (Gurbuz et al., 2011). Moreover, recent investigation recommended the use of doxazosin for children to get rid of stone within a shorter period and consequently diminish the frequency of colic attacks and the need for using analgesics (Erturhan et al., 2013). Furthermore, a recent pilot study suggests that rapid titration of doxazosin is effective in reducing cocaine use (Shorter et al., 2013). In addition to the above-mentioned data concerning the effects of doxazosin, very recent experimental and pre-clinical evidence discuss the impact of α-adrenoceptor antagonists on prostate cancer (Wade et al., 2019).

Therapeutic doses of doxazosin administered orally show rapid and well absorption with peak blood levels attained within 2-3 hours. The bioavailability of doxazosin is about 65%. Approximately 98% of the drug is bound to plasma proteins (Elliott et al., 1987). Doxazosin exhibits biphasic elimination with a terminal plasma elimination half-life of about 10-12 hours for single doses. However, after multiple doses, the terminal half-life was reported to be 22 hours measured beyond 24 hours of drug intake (Elliott et al., 1987; Vincent et al., 1986). Therefore, the drug can be administered as a single daily morning or evening dose. Doxazosin is extensively metabolized in the liver, and only about 5% of the dose excreted in urine as the unchanged drug (Elliott et al., 1987). Hepatic impairment caused no significant alteration in drug pharmacokinetics, namely $C_{max}$ and $T_{half}$ (Elliott et al., 1987; Penenberg et al., 2000). No significant change in drug pharmacokinetics was reported in patients with renal impairment (Elliott et al., 1987; Carlson et al., 1986). The pharmacological effect of doxazosin is directly related to the parent drug only with no evidence of metabolites contribution to drug activity (Elliott et al., 1987). Administration of doxazosin within the clinically used dosage of 1-16 mg daily showed linear (dose-independent) pharmacokinetics (Elliott et al., 1987, 1986). No major variation in drug pharmacokinetics was reported after doxazosin taken by elderly patients (Elliott et al., 1987; Vincent et al., 1986). High-fat meal intake has a little or negligible effect on doxazosin pharmacokinetics and bioavailability (Elliott et al., 1987; Conway et al., 1993). Doxazosin can be given as a single daily morning or evening dose since it was found that the pharmacokinetics and safety of doxazosin were equivalent with morning and evening dosage regimens (Vashi et al., 1996; Kirby et al., 1998).

Despite the common and wide usage of doxazosin worldwide, however, no recent investigations introduced the linearity in the pharmacokinetics of the drug after the therapeutic dose range. Moreover, no published data is available up to date describing the pharmacokinetic behaviors of the drug in the Iraqi population after the administration of therapeutic doses of the drug. Therefore, the current study was conducted to assess the pharmacokinetics of doxazosin in Iraqi healthy male adult subjects after the therapeutic dose range of 2-8 mg tablets.

MATERIALS AND METHODS

Study design

The study was performed in accordance with ICH guidelines for good clinical practice (ICH Guideline for Good Clinical Practice, 1996) and the declaration of Helsinki (Latest WMA Declaration of Helsinki, 2013). As per these guidelines, a study protocol including all details of the study and the informed consent form were prepared by the principal investigator and then reviewed and approved by the clinical investigator and the institutional review board (IRB) before conducting the study. The consent procedure was carried out by the clinical staff under the supervision of the principal investigator and the clinical investigator. All details of the study were thoroughly explained to the subjects who are willing to participate in the study. The participants together with two witnesses and the clinical investigator personally signed two original copies of the consent form, one copy was given to each participant and the other copy was saved in the study file as a source document.

As per the study protocol, 34 healthy adult male Iraqi subjects with ages between 18-48 years and body mass index of 18-30 kg/m² were enrolled in the study. The subjects were judged healthy and considered eligible for participation based on the
following inclusion criteria: normal physical examination, normal clinical examinations including vital signs (blood pressure, pulse, and temperature), electrocardiogram (ECG), medical history (absence of cardiovascular, pulmonary, renal, hepatic, gastrointestinal, hematological, endocrinological, immunological, dermatological, neurological, and psychiatric diseases), and normal clinical laboratory tests including biochemistry, hematology, routine urine analysis, and negative for hepatitis (B & C) and HIV.

The subjects were prohibited from participation based on the following exclusion criteria: heavy smokers (more than 10 cigarettes a day), had acute illness one week before dosing, history of alcohol or drug abuse, history of allergy or contraindications to doxazosin and any related drugs, hospitalization/blood denotation or participation in any clinical trials (pharmacokinetic, bioavailability or bioequivalence studies) by less than two months of the study, consumption of grapefruit containing beverages before one week of the study.

Any subject was allowed to withdraw from the study at any time he wish. Bedside, subject participation was terminated at any time during the study according to the decision of the principal and/or clinical investigators such as violation from the study protocol and for the well-being of the subject.

The selected participants were admitted to the clinical site at about 7 p.m. the day before dosing to the clinical site for blood sampling at 36, 48, 60, and eventually at 72 hours post-dosing. The subjects returned to the clinical site for preparing the subjects and obtaining vital signs. The subjects were conﬁned at the clinical site at about 7 p.m. the day before dosing to the clinical site for blood sampling at 36, 48, 60, and eventually at 72 hours post-dosing.

The vital signs (blood pressure, pulse and temperature) were registered for each subject at about 1.0 hour before drug administration and then after 2.0, 4.0, 8.0, 12, and at 24 hours post-dosing. Clinical examinations, vital signs, and clinical laboratory tests (biochemistry, hematology and routine urine analysis) were also achieved for each subject at the end of each period (72 hours post-dosing). The clinical investigator and the medical staff were available during the entire study to observe, handle, and document any adverse events, adverse drug reactions, and serious adverse effects. Besides, clinical facilities were also available to handle any problem, emergency or unexpected adverse events beyond the capability of the medical staff.

Before about one hour of investigational drug administration, an indwelling cannula was placed in the subject forearm antecubital vein. Five milliliters of blood samples were withdrawn from each subject at zero time (pre-dosing) and then at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, 36, 48, 60, and eventually at 72 hours post-dosing. The blood samples were immediately transferred to heparinized tubes and centrifuged at 4000 rpm for 5 minutes to separate the plasma. The plasma samples were directly placed in Eppendorf tubes by polypropylene Pasteur pipettes and saved at -30±10°C. After each blood sample withdrawal, 0.5 ml saline containing 20 units/ml of heparin was flushed into the cannula to prevent blood clotting and closure of the cannula. Moreover, before each blood sampling withdrawal, about 0.2 ml of blood was discarded from the cannula to get rid of any residual blood from a previous blood sample. Eighteen blood samples were obtained from each subject during each study period. The in-house confidential system was followed for labeling the Eppendorf tubes, which indicate: study protocol number, subject number, and blood sampling time. The principal investigator and the quality assurance responsible only had access to the key of the labeling system.

**Determination of doxazosin in plasma**

Concentrations of doxazosin in the plasma samples obtained from each subject were determined by HPLC and fluorescence detection method (Kim et al., 2006). The analytical method was validated according to FDA Bioanalytical Method Validation Guidance (Guidance For Industry, FDA, 2001; Bioanalytical Method Validation Guidance, FDA, 2018). The method validation included: accuracy and precision for inter- and intraday variations, sensitivity, specificity/selectivity linearity, recovery, and stability. The linearity of the standard calibration curve was established for concentrations range from 0.3-50 ng/ml with a lower limit of quantification (LLOQ) of 0.3 ng/ml plasma using propranolol as internal standard (Kim et al., 2006). For determination of doxazosin concentrations in the unknown authen-
tic samples, each analytical run (batch) included plasma samples obtained from each subject at each period, standard calibration curve and quality control (QC) samples (low, medium & high). Doxazosin plasma concentrations were not determined by extrapolation below the LLOQ or above the upper limit of quantitation (ULOQ) of the standard calibration curve. Doxazosin plasma concentrations above the ULOQ were determined by dilution according to the applied bioanalytical method validation. Assay of doxazosin in all collected plasma samples were achieved after completing the clinical phases of the study (at the end of period 3) as recommended by the above FDA guidance.

**Pharmakikinetic and statistacal analysis**

Kinetica software was used for all pharmacokinetic calculations and statistical analysis. Microsoft Excel was used for data plotting and descriptive statistics. From plasma concentration-time data of each subject, the pharmacokinetic parameters $C_{\text{max}}$, $AUC_{0-t}$, $AUC_{0-\infty}$, $T_{\text{max}}$, $K_{\text{elimination}}$, and $T_{1/2}$ were calculated according to standard methods applying non-compartmental data analyses (Shargel and Andrew, 2012; Malcolm and Thomas, 2011). Maximum or peak blood concentration ($C_{\text{max}}$) and the time to achieve $C_{\text{max}}$ ($T_{\text{max}}$) were obtained directly from the concentration-time curve. The terminal elimination rate constant ($K_{\text{elimination}}$ or $\lambda_2$) was determined by linear regression of at least three last points at the terminal phase of the log concentration-time curve. The terminal elimination half-life ($T_{1/2}$) was measured as $0.693/\lambda_2$. Trapezoidal rule was used for calculating the area under the concentration-time curve ($AUC_{0-t}$) from time zero ($t_0$) to the last time ($t_{\text{last}}$) at which last measurable concentration ($C_{\text{last}}$) was detected. The $AUC_{t-\infty}$ is the extrapolated ($AUC_{\text{extrapolated}}$) or residual ($AUC_{\text{residual}}$) area under the plasma concentration-time curve from $t_{\text{last}}$ to infinity was calculated as $C_{\text{last}}/\lambda_2$. The $AUC_{0-\infty}$ is an area under the concentration-time curve from $t_0$ to $t_{\infty}$ was calculated from the sum of $AUC_{0-t}$ and $AUC_{t-\infty}$. The % extrapolated AUC was calculated as $(AUC_{t-\infty}/AUC_{0-\infty}) \times 100$. The pharmacokinetic calculations were achieved applying international guidance and criteria and their updated versions (Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, FDA, 2013; European Medicines Agency, EMEA, 2010). All statistical data analysis including descriptive statistics (mean, standard deviation (SD), coefficient of variation (CV), correlation coefficient (r) and median) were performed following standard statistical approaches (Shein-Chung and Jen-Pei, 2000; Statistical Approaches to Establishing Bioequivalence, FDA, 2001).

**RESULTS AND DISCUSSION**

All steps of the present investigation, including clinical, bioanalytical, pharmacokinetic and statistical analysis were performed according to a study protocol which was submitted and approved according to international guidelines and criteria before conducting the study. No violations or deviations from the study protocol were documented throughout the entire study.

Figure 1: Plasma concentrations-time profile (Mean±SD)

Figure 2: Plasma concentrations-time profile (Mean±SD)

Doxazosin is available as 1, 2, 4 and 8 mg tablets. The therapeutic dose range for the treatment of hypertension is 1-16 mg once daily, and the maximum recommended daily dose is 16 mg once daily. For the treatment of benign prostatic hyperplasia (BPH), the therapeutic dose range is 1-8 mg once...
Table 1: Demographic data of 30 males participated in the study

<table>
<thead>
<tr>
<th>Demographic properties</th>
<th>Mean±SD</th>
<th>%CV</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.9±8.1</td>
<td>26.9</td>
<td>19-45</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>76.8±10.2</td>
<td>13.3</td>
<td>61-89</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.69±0.08</td>
<td>4.7</td>
<td>1.57-1.80</td>
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</tbody>
</table>

Table 2: Pharmacokinetic parameters of doxazocin after administration of 2, 4 and 8 mg doxazocin to 30 healthy male adults fasted subjects

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>2 mg Mean ± SD (%CV)</th>
<th>4 mg Mean ± SD (%CV)</th>
<th>8 mg Mean ± SD (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>16.0±3.9 (24.0)</td>
<td>30.6±6.7 (21.9)</td>
<td>63.5±16.5 (25.7)</td>
</tr>
<tr>
<td>AUC0-t (ng.hr/ml)</td>
<td>235.9±41.8 (17.7)</td>
<td>464.8±72.3 (15.6)</td>
<td>958.2±170.2 (17.8)</td>
</tr>
<tr>
<td>AUC0–∞ (ng.hr/ml)</td>
<td>260.5±60.6 (23.3)</td>
<td>497.0±71.1 (14.3)</td>
<td>1050.9±240.8 (22.9)</td>
</tr>
<tr>
<td>%AUCextrapolated</td>
<td>8.2±2.0 (24.6)</td>
<td>6.7±1.7 (25.4)</td>
<td>7.2±1.9 (26.4)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>1.95±0.91 (46.7)</td>
<td>1.74±0.71 (40.8)</td>
<td>2.01±0.89 (44.3)</td>
</tr>
<tr>
<td>(1.67)b (0.67-3.0)c</td>
<td>1.67b (0.67-3.0)c</td>
<td>1.67b (0.67-3.0)c</td>
<td></td>
</tr>
<tr>
<td>Thalf</td>
<td>15.1±4.0 (26.5)</td>
<td>16.5±3.7 (22.4)</td>
<td>14.9±4.1 (27.5)</td>
</tr>
</tbody>
</table>

Table 3: Pharmacokinetic parameters of doxazocin presented in previous studies after administration of 2, 4 and 8 mg doxazocin to healthy adult fasted subjects

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>2 mg Mean ± SD</th>
<th>4 mg Mean ± SD</th>
<th>8 mg Mean ± SD</th>
<th>4 mg Mean ± SD</th>
<th>4 mg Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>13.7±2.9</td>
<td>29.3±8.4</td>
<td>66.8±17.6</td>
<td>41.5±10.9</td>
<td>47.7±NAc</td>
</tr>
<tr>
<td>AUC0–∞ (ng.hr/ml)</td>
<td>195±45</td>
<td>NA</td>
<td>499.1±129.9</td>
<td>743.4±149.5a</td>
<td></td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2.0±0.8</td>
<td>3.7±1.5</td>
<td>3.9±1.2</td>
<td>1.7±0.8</td>
<td>3.0±1.0</td>
</tr>
<tr>
<td>Thalf (hr)</td>
<td>14.0±3.6</td>
<td>NA</td>
<td>20.5±6.1</td>
<td>10.2±1.8</td>
<td>18-20b</td>
</tr>
<tr>
<td>Reference</td>
<td>(Chung et al., 1999)</td>
<td>NA</td>
<td>(Chung et al., 1999)</td>
<td>(Sayam et al., 2007)</td>
<td>(Ma et al., 2007)</td>
</tr>
</tbody>
</table>

*dNo significant difference (p>0.05) based on ANOVA, *Median, cRange.

Daily, and the maximum recommended dose is 8 mg daily (*Cardura®*, 2016). The linearity in the pharmacokinetics of doxazosin at doses 1-16 mg was reported previously (*Elliott et al., 1986, 1987*). No recent study concerning the assessment of linearity in doxazosin pharmacokinetic was published up to date. Besides, no published data is available to date regarding the pharmacokinetic characteristics of the drug in the Iraqi population. Therefore, the current study was conducted to assess the pharmacokinetics of the drug in Iraqi healthy male adult subjects after therapeutic dose ranges of 2-8 mg tablets.

Thirty-four subjects enrolled in the study; however, 4 subjects withdrew for personal reasons. All the thirty subjects completed the study were discharged without any changes in their clinical baseline characteristics, including vital signs (blood pressure, pulse, and temperature), electrocardiogram (ECG), and clinical laboratory tests (biochemistry, hematology, and routine urine analysis).
Figure 3: Plasma concentrations-time profile (Mean±SD)

Figure 4: Mean plasma concentrations-time profiles of doxazosin

Figure 5: Log mean plasma concentrations-time profiles of doxazosin

Figure 6: Correlation between dose range 2-8 mg and $C_{\text{max}}$ (Mean±SD)

Figure 7: Correlation between dose range 2-8 mg and $\text{AUC}_{0-t}$ (Mean±SD)

Figure 8: Correlation between dose range 2-8 mg and $\text{AUC}_{0-\infty}$ (Mean±SD)
Figures 1 and 2 and Figure 3 present the mean±SD for plasma concentrations versus time profiles of doxazosin plotted in rectilinear graphs after administration of 2, 4, and 8 mg, respectively. Figure 4 and Figure 5 introduce the mean plasma concentration versus time profiles of doses 2, 4 and 8 mg plotted in rectilinear and semilog graphs, respectively. Figures 6 and 7 and Figure 8 show the correlation between doses 2, 4, and 8 mg of doxazosin with their corresponding \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \). Table 1 summarizes the demographic characteristics of the subjects who participated in the study. Table 2 demonstrates the pharmacokinetic parameters of the drug after administration of the investigated doses 2, 4, and 8 mg.

The pharmacokinetic parameters \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \) increase proportionally with their corresponding doses 2, 4, and 8 mg (Table 2). Dose normalization of these parameters (a division of the parameter with the corresponding dose) demonstrated statistically no significant difference applying ANOVA test (p>0.05). Moreover, the ANOVA test showed no statistically significant difference (p>0.05) for the pharmacokinetic parameters \( T_{\text{max}} \) and \( T_{\text{half}} \) over the investigated dose range of the drug. Besides, good positive correlations were found between doses 2, 4, and 8 mg of doxazosin with their corresponding \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \) with correlation coefficient \((r^2)\) approaching 1.0 as depicted in Figures 6 and 7 and Figure 8, respectively. Thus, these findings indicate that doxazosin exhibits linear pharmacokinetics over the investigated dose ranging from 2-8 mg.

The pharmacokinetic parameters calculated in this investigation, \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( T_{\text{half}} \), exhibited relatively low variations between subjects with a % coefficient of variations (%CV) of 20-30%. However, \( T_{\text{max}} \) showed higher interindividual variation since the %CV was about 40% (Table 2). The calculated % \( \text{AUC}_{\text{extrapolated}} \) had negligible contribution (less than 10%) of the total \( \text{AUC} \) (\( \text{AUC}_{0-\infty} \)), indicating that blood sampling for 72 hours post-dosing is adequate enough for reliable estimation of doxazosin pharmacokinetic parameters after therapeutic dose ranges of 2-8 mg (Table 2). Besides, a lower limit of quantification (LLOQ) of 0.3 ng/ml used is also sufficient for reliable determination of the termination elimination half-life of the drug.

The pharmacokinetic parameters presented in other investigations are summarized in Table 3.

The average \( C_{\text{max}} \) values after 2, 4, and 8 mg doses estimated in the current study are almost comparable to that presented in the literature (Chung et al., 1999). The average \( C_{\text{max}} \) value of 4 mg dose (Table 2) is almost 35% lower than that reported for Thai and Chinese healthy adult subjects (Sayam et al., 2007; Ma et al., 2007), as shown in Table 3. However, the mean \( \text{AUC}_{0-\infty} \) for Thia subject (Table 3) is similar to that found in Iraqi subjects (Table 2). Interestingly, the ranges of \( T_{\text{max}} \) and \( T_{\text{half}} \) values found in the current study are approximately similar to that introduced in all previous investigations Pharmacokinetic parameters of doxazocin presented in previous studies after administration of 2, 4 and 8 mg doxazocin to healthy adult fasted subjects (Chung et al., 1999; Sayam et al., 2007; Ma et al., 2007).

CONCLUSIONS

The present investigation demonstrated that the pharmacokinetics of doxazosin in Iraqi healthy male adult subjects shows linear pharmacokinetics over the therapeutic dose ranges of 2-8 mg. Besides, The pharmacokinetic parameters \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( T_{\text{half}} \) exhibited low interindividual variation of about 25%. However, \( T_{\text{max}} \) showed a higher variation of about 40%.

ACKNOWLEDGEMENT

The authors are very grateful to all subjects participated in the study. The authors are also very thankful to the clinical and analytical staff. Special thanks and appreciation to Dr. Zahraa Al-Tamimi and Manar Al-Tamimi for their technical assistance in editing this article.

REFERENCES


Cardura® 2016. Date of Revision. Pfizer Products Inc. Monograph.

Carlson, R. V., Bailey, R. R., Begg, E. J., Cowlishaw,


Shein-Chung and Jen-Pei 2000. Design and Analysis of Bioavailability and Bioequivalence Studies.


