Pharmacokinetic and bioequivalence studies of fast dispersible ketoprofen tablets in healthy volunteers

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Abstract: In the present study the pharmacokinetic and bioequivalence parameter of Ketoprofen 100 mg fast dispersible tablets (test) were measured with marketed (reference) product. This study was accomplished following FDA guidance. A single dose, open labeled, cross over (two way), randomized study design was used to conduct investigation on 12 Pakistani healthy volunteers. At various time points blood samples (10mL) were drawn i.e. at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12 and 13hr. Plasma was then separated and ketoprofen concentrations were estimated by validated HPLC technique using LC 20A pump (Shimadzu Corp, Japan) and Spectrophotometric SPD-20Adetector (Shimadzu Corp, Japan). Ketoprofen concentrations were then analyzed by Kinetica™ 4.4.1 (Thermo electron corp, USA) to estimate various compartmental and noncompartmental pharmacokinetic parameters. Various parameters of bioequivalence including AUC0-t, AUC0-∞, Tmaxcalc, Cmaxcalc, Tlast, Clast were compared using ANOVA method (two way). For log and non-log transformed data the 90 % confidence interval values for AUC0-∞ (1.0087-1.0704; 1.0099-1.0714), AUC0-t (0.95482-1.0093; 0.95486-1.0098), AUClast (0.93373-0.98605; 0.93404-0.98603), Cmaxcalc (0.92978-0.9955; 0.92962-0.99663) and Tmaxcalc (0.89019-0.94116; 0.89095-0.94288) for test and reference products respectively. Results were found to be within the FDA satisfactory range. For the results verification, Schuirman’s one sided t test was used. SPSS 17.0 (SPSS Inc) was utilized for the determination of wilcoxon sign rank test. Results showed no carry over effect after first study period. Also test product met the regulatory criteria for bioequivalence with the reference product. Both the formulations were well tolerated.

Keywords: Ketoprofen, randomized, compartmental method, non-compartmental method and log transformed.

INTRODUCTION

Different scientists reported that variations in manufacturing methods as well as the differences in the composition of pharmaceutical dosage forms can influence the bioavailability of the product. It can also be affected by different factors particularly patient physiology, blood flow, gastrointestinal tract (GI) transit rate, condition of GI tract membrane, metabolism in gastrointestinal tract during the first pass effect, age, race, sex etc also manufacturing and formulations variables such as dosage form composition and compression force. Also most of the drugs cannot be taken as pure compounds but are manufactured in to different dosage forms. Differences in the manufacturing and formulation variables could influence the bioavailability of the product (Shoaib et al., 2008). Therefore, bioequivalence study is considered to be one of the important in vivo quality assessments for the drug product and also it is issued as a surrogate for therapeutic efficacy (Blume et al., 1994).

Ideal dosage forms should deliver therapeutic drug concentrations, reducing both quantity, frequency and enhancing patient compliance (Bhatt and Vaidya, 1992). Fast dispersible tablets are rapidly disperse in water which can be easily swallowed by the patient (Martin et al., 1993). Dispersible tablets were developed for those patients who have difficulty in swallowing the capsules and tablets (Wilson et al., 1987). Different strategies were adopted for the manufacturing of fast dispersible products of various compounds (Chang et al., 2000) to offer a suitable resolution for such patients (Fu et al., 2004; Sunada et al., 2002). Therefore, drug release pattern is considered to be one of the most important parameter for such type of dosage form because alterations in the release pattern will produce its impact on absorption rate which finally influence the therapeutic efficiency (Lima et al., 2008).

Ketoprofen is widely used as an anti-inflammatory compound with pronounced analgesic and antipyretic properties. It is prescribed for the treatment of rheumatoid arthritis, osteoarthritis and musculoskeletal problems (Anderson et al., 1998). Ketoprofen is weakly acidic ionized compound. It is slightly soluble in water. At pH 6.8 the drug solubility found to be high (Sheng et al., 2006). Maximum plasma levels achieved within 0.5-2 hrs, after which drug concentration in plasma falls rapidly. It is eliminated from the body following first order kinetics with elimination half-life between 1.5-2 hrs (Upton et al., 1981).

In present study, pharmacokinetic and bioequivalence study was conducted on the selected fast dispersible Ketoprofen tablets, which was developed earlier and reported (Zafar et al., 2012). The pharmacokinetic
features of ketoprofen have been previously reported (Roda et al., 2002) but no pharmacokinetic data is available for the fast dispersible formulation of ketoprofen in the healthy Pakistani population. The purpose of the presented work is to evaluate different pharmacokinetic parameters of the dispersible formulation and to compare the in vivo behavior of the test (dispersible ketoprofen tablets) with reference formulation (conventional) in male healthy Pakistani volunteers.

MATERIAL AND METHODS

Materials
Fast dispersible tablets containing 100mg of Ketoprofen (test) and immediate release (core tablet containing 100 mg of Ketoprofen produced by Sanofi Aventis, Pakistan, as the reference product).

Chemical and reagents
HPLC grade Methanol and Ortho-Phosphoric Acid (Merck, Darmstadt, Germany), and Membrane Filters (0.45µ - 47mm & 13mm diameter Millipore, England).

Instrumentation
Analyses were executed using chromatographic system composed of LC 20A pump, detector(spectrophotometric) SPD-20A (Shimadzu Corp, Japan), Communication Module (CBM 102) with Class GC software (GC 20), Shimadzu Corp, Japan. Guard column &C18 column Discovery HS (5µm (250mm x 4.6mm), Vortex Mixer (Whirl, England), Centrifuge machine (Osterode, Hereues, Germany), swinney (Millipore, England) were utilized for the estimation of results.

Pharmacokinetic and bioequivalence study

Study population and volunteers selection
In present study, the pharmacokinetic parameters of test (F6) and reference formulation manufactured by Novartis Pakistan, were carried out in 12 healthy volunteers. The pharmacokinetic and bioequivalence study was also conducted following FDA guidelines. The study approval was obtained by the Ethics Review Committee, Ziauddin University, Karachi, Pakistan. An open label, single dose, single centre, randomized, cross over pharmacokinetic study was conducted with two week washout period. Volunteers were already informed about the study and a written consent was taken from all the subjects. Subjects were selected having an age group (22-26 years); weighing (65-70kg), height (5.5-6.0ft. in). Selection of subjects was made according to the FDA guidelines (www.fda.gov).

Prior to the study all the subjects were assessed by a medical practitioner and there medical history was taken. Subjects should have no medical disorders and should not be hypersensitive to the active compound (ketoprofen). Volunteers were evaluated for hepatic, haemopoetic and renal functions tests before being included in the study. All the selected volunteers were healthy following medical history, laboratory assessments and physical examination. The volunteers were notified about the protocol of the study design and were not allowed to use any medicine within 2 weeks prior to the former study period until the end of the next study period. Selected volunteers should have no tendency of drinking beverages having alcohol or smoking. Volunteers were not allowed to eat (any food) and drink (containing alcohol, methylxanthines and caffeine) 48 hours before the initiation of sample collection till the completion of both study periods.

Fig. 1: Average Ketoprofen plasma concentration time profiles of test and reference formulations in twelve healthy volunteers. Bars indicate mean standard error.

Study design and sampling protocols
In this study the optimized fast dispersible ketoprofen 100 mg formulation (F6) (Zafar et al., 2012) were selected as a test formulation whereas marketed formulation was used a reference product for the present pharmacokinetic and bioequivalence study. During the first study period, each volunteer has orally administered single tablet of reference formulation (100mg) with 250 ml of water. All the subjects were asked to fast overnight (12 hours). After two weeks washout period, second study period was conducted in which test formulation (100mg) was dispersed in water (250mL) and then it was administered by the volunteers subsequently after an overnight fast. During the study period standardized conditions were maintained for the subject’s i.e. environmental conditions, physical activity and diet.

In both study periods, blood samples were drawn by venipuncture. Cannula was inserted into the forearm of each volunteer for collection of samples. Initially blood sample (10mL) was collected before drug administration while the further (ten mL each) were drawn at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12 and 13 hours.

Heparinized tubes were used for blood samples. Plasma separation was carried out by centrifugation of all samples for 10 minutes at 3500 rpm. Using sterilized tubes samples were stored at -20°C. Plasma was separated from
protein using equal portions of acetonitrile (ACN) and plasma (1:1 ratio) followed by vortexing and centrifugation (3,500rpm for 10min). Using 0.45μ membrane filter, supernatant was filtered and placed in swinney. Filtered samples were then injected in the Rheodyne Loop of chromatographic system in 100μL volume for estimation.

**Plasma drug analysis**

In this study a validated isocratic (High Performance Liquid Chromatography) HPLC procedure, which was reported for the estimation of ketoprofen in plasma samples. For this purpose, the isocratic HPLC mobile phase composed of Methanol: Water (70: 30 v/v) with pH 3.3, adjusted with phosphoric acid. Flow rate was adjusted 1mL min⁻¹. Estimation was carried out at 260 nm and the total run time is 10 min (Zafar et al., 2013).

**Pharmacokinetic and bioequivalence statistical analysis**

In this study compartmental and noncompartmental assessment for test and reference formulations were carried out by utilizing Kinetica™ soft ware version 4.4.1 (Thermoelectron, USA) (Kinetica™ User Manual, 2005). Data was excellently fitted to oral two-compartment model and several compartmental attributes (Kₑᵣ, α, β, Kᵢ, B, A, Tᵢ/₂Ka, Cᵢ/₂maxcalc, AUCᵢ₀₋ᵣ, Kᵢ₂, Tᵢ₂/₀, Tᵢ₁/₂Kel, Tᵢ₁/₀, Tᵢ₁/₂Ka, Vᵢ, CI and Tᵢlog) were assessed. Similarly, various noncompartmental features were also evaluated (MRT, AUMC, L₂₅, AUCᵢ₀₋ₙ, AUCᵢ₀₋ₙ₉₅₆₉₉₅₆, AUMCᵢ₀₋ₙ₉₅₆₉₉₅₆, Vᵢ, Tᵢ₉₉₅₆₉₉₅₆₉₉₅₆ and Cᵢ₉₉₅₆₉₉₅₆).

Bioequivalence parameters i.e. AUCᵢ₀₋ᵣ, AUCᵢ₀₋ₙ, Cᵢ₉₉₅₆₉₉₅₆, AUCᵢ₀₋ₙ₉₅₆₉₉₅₆, and Tᵢ₉₉₅₆₉₉₅₆calc of both products were subsequently evaluated using two way ANOVA methods. To verify bioequivalence evaluation, Schirmann’s two-one sided t test was also applied. Bioequivalence of the products may be proven by using confidence interval (CI) values 90 % for both trial and reference formulations, if the ratio of the values lied in order of 0.8-1.25 and 0.8-1.20 for log transformed and non log transformed data respectively. Wilcoxon Sign Rank, (non parametric assessment) was also determined for the estimation of carry over effect using statistical software SPSS 20.0 (SPSS Inc).

**RESULTS**

**Pharmacokinetic parameters**

Fig. 1 presents average Ketoprofen concentration (plasma) time profiles of test and marketed formulations in twelve volunteers. Table 1 and 2 presents the average values of both compartmental and noncompartmental parameters in 12 volunteers for marketed and test products.

**Bioequivalence evaluation**

Bioequivalence estimation was carried out by comparing test and reference products with respect to AUCᵢ₀₋ᵣ, AUCᵢ₀₋ᵣ₉₉₅₆₉₉₅₆, AUCᵢ₀₋ₙ₉₅₆₉₉₅₆, Tᵢ₉₉₅₆₉₉₅₆calc and Cᵢ₉₉₅₆₉₉₅₆ using two way ANOVA method. The mean log-transformed and non-transformed data of above parameters and their 90% confidence interval (CI) values were fell within the range of 0.8-1.25 % as shown in table 3. Furthermore, two one sided t test (Schirmann’s) was applied to authenticate bioequivalence evaluation as shown in table 4. To observe the carry over effect of the drug, Wilcoxon Sign Rank test for Tᵢ₉₉₅₆₉₉₅₆ was used and results indicated insignificant effect of carry over, with the value of< 13 for rank sum (table 5).

**DISCUSSION**

In the present study pharmacokinetic assessment (compartmental and noncompartmental) were carried out by analyzing various parameters as presented in tables 1 and 2. The mean values of AUCᵢ₀₋ᵣ, AUCᵢ₀₋ₙ₉₅₆₉₉₅₆ and AUCᵢ₀₋ₙ₉₅₆₉₉₅₆ observed insignificantly different for both test and reference formulations. The mean AUCᵢ₀₋ᵣ values were found to be (reference, 24,995±1.010 mg/Lh; test, 26,011±1.819mg/Lh). Values of Cᵢ₉₉₅₆₉₉₅₆ and Tᵢ₉₉₅₆₉₉₅₆ helps in assessing the results of pharmacokinetic studies (Rosenbaum, 2011). The calculated value of mean Cᵢ₉₉₅₆₉₉₅₆ (reference, 2.865±0.071µg mL⁻¹; test, 2.759±0.152µg mL⁻¹) were found to be similar to other author’s reported (Dollery, 1991; Lewellen and Templeton, 1976; Ishizaki et al., 1980). Similarly, Roda et al. in 2002 carried out pharmacokinetic study of prompt release Ketoprofen capsules 100mg (ibifen) having 12 hourly administrations; Cᵢ₉₉₅₆₉₉₅₆ and Tᵢ₉₉₅₆₉₉₅₆ were found to be 8-12µg mL⁻¹ and 1.5-2 hrs respectively. Also AUC was 66.33±11.78µg. h/mL. In the present study based on the average Tᵢ₉₉₅₆₉₉₅₆ values (reference, 1.719±0.092 hr; test, 1.576±0.129 hr), time to achieve onset of action was found to be earlier with the dispersible formulation. It is generally found that orally disintegrating tablets showed rapid absorption than a conventional formulation because of the rapid disintegration (Chen et al., 2009). Clearance (constant) showing correlation between plasma concentration and elimination rate (Rosenbaum, 2011). Mean CI and Vᵢ values were in order of; reference, 4.006±0.160 L/hr⁻¹ and 16.521±0.781 L correspondingly; test, 3.86±0.276 L/hr⁻¹ and 15.526±1.517 L respectively) similar findings were also reported by other authors. Researchers found similar results for volume of distribution and clearance following intravenous administration of Ketoprofen (Kokki et al., 2003; Rençber et al., 2009). Whereas, rate constants kᵢ and Kᵢ (reference, 0.963±0.094 hr⁻¹ and 0.242±0.012 hr⁻¹ respectively; test, 0.912±0.170 hr⁻¹ and 0.249±0.013 hr⁻¹ respectively). Similarly, elimination half livesTᵢ₁/₂Kel (reference, 0.725±0.077 hr; test, 0.787±0.167 hr), Tᵢ₁/₂Ka (reference, 2.860±0.141h; test, 2.784±1.817h) were determined. Similar results were reported by Ishizaki et al. after oral and intramuscular administration of ketoprofen in human volunteers. Different scientists found higher Cᵢ₉₉₅₆₉₉₅₆ values (50 %), 15 min earlier Tᵢ₉₉₅₆₉₉₅₆ values and higher AUC values 68 % for lyophilized Ketoprofen formulation as compared to the marketed formulation (Ahmed et al., 2007). Also other noncompartmental
Pharmacokinetic and bioequivalence studies of fast dispersible ketoprofen tablets in healthy volunteers

Table 1: Mean compartmental parameters of Ketoprofen after administration of Reference and Test formulations to 12 male healthy volunteers. S.D. = standard deviation and C.V. = coefficient of variation

<table>
<thead>
<tr>
<th>Reference</th>
<th>SD</th>
<th>% CV</th>
<th>Test</th>
<th>SD</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kₑ</td>
<td>0.9</td>
<td>0.0</td>
<td>9.8</td>
<td>0.1</td>
<td>18.</td>
</tr>
<tr>
<td>Kᵣ</td>
<td>0.2</td>
<td>0.0</td>
<td>5.3</td>
<td>0.2</td>
<td>62.</td>
</tr>
<tr>
<td>A</td>
<td>4.2</td>
<td>0.3</td>
<td>44</td>
<td>0.4</td>
<td>984</td>
</tr>
<tr>
<td>α</td>
<td>0.8</td>
<td>1.2</td>
<td>368</td>
<td>0.9</td>
<td>11</td>
</tr>
<tr>
<td>B</td>
<td>1.7</td>
<td>0.1</td>
<td>74</td>
<td>1.5</td>
<td>16.</td>
</tr>
<tr>
<td>β</td>
<td>0.09</td>
<td>0.01</td>
<td>0.07</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>F_max</td>
<td>24.9</td>
<td>6.0</td>
<td>10.2</td>
<td>11.</td>
<td>17.</td>
</tr>
<tr>
<td>C_max</td>
<td>95</td>
<td>1.00</td>
<td>5</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>T_max</td>
<td>1.71</td>
<td>0.09</td>
<td>5.38</td>
<td>0.12</td>
<td>5.54</td>
</tr>
<tr>
<td>Vₚ</td>
<td>16</td>
<td>0.07</td>
<td>4.7</td>
<td>1.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Kₑ/α</td>
<td>0.3</td>
<td>0.0</td>
<td>15.6</td>
<td>0.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Kᵣ/β</td>
<td>0.7</td>
<td>0.2</td>
<td>9.5</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>T₁/₂ₑ/α</td>
<td>16</td>
<td>0.1</td>
<td>2.8</td>
<td>1.0</td>
<td>3.6</td>
</tr>
<tr>
<td>T₁/₂ᵣ/β</td>
<td>25</td>
<td>0.0</td>
<td>71</td>
<td>0.7</td>
<td>8.7</td>
</tr>
<tr>
<td>T₁/₂ᵣ/α</td>
<td>3.6</td>
<td>0.8</td>
<td>1.1</td>
<td>1.1</td>
<td>4.9</td>
</tr>
<tr>
<td>T₁/₂ₑ/β</td>
<td>7.7</td>
<td>0.0</td>
<td>2.8</td>
<td>0.0</td>
<td>4.3</td>
</tr>
<tr>
<td>CI</td>
<td>2.8</td>
<td>4.0</td>
<td>0.2</td>
<td>78</td>
<td>704</td>
</tr>
</tbody>
</table>

Table 2: Mean non- compartmental parameters of Ketoprofen after administration of Reference and Test formulations to 12 male healthy volunteers. S.D. = standard deviation and C.V. = coefficient of variation

<table>
<thead>
<tr>
<th>AUMC</th>
<th>MRT</th>
<th>L₂</th>
<th>Vₚ</th>
<th>AUMC_lat</th>
<th>AUMC_int</th>
<th>AUMC_lat</th>
<th>AUMC_int</th>
<th>t_max</th>
<th>t_max</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/Lx(h)^2</td>
<td>h</td>
<td>l/h</td>
<td>L</td>
<td>mg/Lx(h)</td>
<td>mg/Lx(h)</td>
<td>mg/Lx(h)</td>
<td>mg/Lx(h)</td>
<td>hr</td>
<td>mg/mL^2/h</td>
</tr>
<tr>
<td>Reference</td>
<td>255.954</td>
<td>9.005</td>
<td>0.112</td>
<td>37.423</td>
<td>18.403</td>
<td>23.924</td>
<td>93.802</td>
<td>215.597</td>
<td>3.128</td>
</tr>
<tr>
<td>SD</td>
<td>40.101</td>
<td>0.608</td>
<td>0.012</td>
<td>3.655</td>
<td>0.424</td>
<td>0.361</td>
<td>2.240</td>
<td>16.858</td>
<td>0.098</td>
</tr>
<tr>
<td>Test</td>
<td>317.829</td>
<td>9.441</td>
<td>0.107</td>
<td>39.983</td>
<td>17.668</td>
<td>23.502</td>
<td>90.452</td>
<td>222.466</td>
<td>3.340</td>
</tr>
<tr>
<td>SD</td>
<td>68.907</td>
<td>0.997</td>
<td>0.015</td>
<td>4.818</td>
<td>0.714</td>
<td>0.975</td>
<td>3.079</td>
<td>31.030</td>
<td>0.090</td>
</tr>
</tbody>
</table>

AUMC = Area under the first moment curve AUMC_lat =AUMC from t=0 to last MRT = Mean residence time AUMC_int = Total AUMC (=AUMC_lat + AUMC_extra) L₂ = Elimination rate constant in non compartmental analysis AUCₚ =AUC last + AUC_extra Vₚ = The apparent volume of distribution during the terminal phase AUMC_lat =AUMC from t=0 to t last

parameters were analyzed i.e., MRT, AUMC, L₂, AUMC_lat, and AUMC_int, as shown in table 2.

Also ANOVA two-way test was conducted using Kinetica software for the comparison of two products. For this reason the Latin Square method was used for statistical estimation of two treatment, two period, randomized crossover study design. According to FDA guidance for bioequivalence estimation different parameters were statistically analyzed by Latin Square ANOVA. The current investigation was conducted to compare the bioequivalence between the two products. The 90% CI for C_max = (0.2798-0.9955), T_max = (0.89019-0.94116), AUC₀-∞ = (1.0087-1.0704), AUC₂₄ = (0.93737-0.98605) and AUC₀-∞ = (0.95482-1.0093) as shown in table 3. Chen et al. in 2009 conducted a bioequivalence study between conventional and orally disintegrating filmsteride products and found 90% CIs for C_max, AUC₀-∞ and AUC₀-∞.

Similarly, Kim et al. in 2011 found similar T_max and T₁/₂ values for conventional and orally disintegrating Donepezil formulations. Also, Huang et al. in 2012 reported that on ANOVA conventional and dispersible tablets of Risperidone showed no significant difference in C_max, AUC₀-∞ and AUC₀-∞. In the present study significant effects were found as P values (probability of Type I error) of T_max = (0.00018; subject 0.003653), AUC₀-∞ = (0.03324; formulation 0.04133), AUC₂₄ = (0.02059). Results of 90% CI for log transformed values for different parameters i.e.
$C_{\text{max}}$, $T_{\text{max}}$ and $\text{AUC}_{0-\infty}$, $\text{AUC}_{\text{last}}$ and $\text{AUC}_{\text{tot}}$ are found to be within the adequate range. Table 4 showed that the results of Schuurman’s one-sided $t$ test. For non-log transformed data, analysis of variance was carried out as $P$ values were $>0.05$ (non significance). Similarly, 90% CI limits were analyzed by geometric means. The geometric mean values and geometric mean ratio of (Test/Reference) of different parameters were shown in Table 3. The 90% confidence interval for non-log transformed values for $\text{AUC}_{0-\infty}$ (1.0099-1.0714), $\text{AUC}_{\text{tot}}$ (0.95486-1.0098), $\text{AUC}_{\text{last}}$ (0.93404-0.98603), $C_{\text{maxcalc}}$ (0.92962-0.99663) and $T_{\text{maxcalc}}$ (0.89095-0.94288) for the test and reference formulations are within the FDA acceptable limits (Gogtay et al., 2003). Liu et al. carried out bioequivalence study between conventional and orally disintegrating flurbiprofen tablets. The 90% CIs (ln-transformed ratios) of $\text{AUC}_{0-\infty}$, $C_{\text{max}}$ and $\text{AUC}_{0-24}$ were found to be in adequate limits. The relative bioavailability of Ketoprofen was found to be 104.064%. Both the formulations were found to be well tolerated. Wilcoxon sign Rank test was used by several authorities to check the drug effect (Rani and Pargal, 2004). In this work statistical software SPSS 17.0 (SPSS Inc), was used to perform Wilcoxon test (Sign Rank) and no carry over effect was observed due to the smaller rank sum value i.e., <13 (Table 5).

CONCLUSION

It was concluded that fast dispersible formulation of Ketoprofen was bioequivalent with the reference marketed brand and have showed faster achievement of maximum concentration of plasma. Such products may be useful for rapid relief of analgesia and inflammatory problems.

REFERENCE

Ahmed IS and Fatahalla FA (2007). Pilot study of relative bioavailability of two oral formulations of Ketoprofen 25mg in healthy subjects. A fast-dissolving lyophilized lyophilized...
tablet as compared to immediate release tablet. Drug Dev. Ind. Pharm., 33: 505-511.


Chang RK, Guo X, Burnside BA and Couch RA (2000).


