COMPARATIVE BIOEQUIVALENCE STUDY OF MELOXICAM DRUGS

The governments of many countries strongly support the production and clinical use of generic medicinal products which are “copies” of patented drugs and can be marked at lower cost. At present time bioequivalence testing is regarded as a useful methodology to perform comparisons among different products containing the same active ingredient. This report presents the results of comparative bioequivalence study of three meloxicam formulations: brand-drug “Melbek” with tablets and capsules of meloxicam developed at the Tashkent Pharmaceutical Institute. The results obtained confirm the bioequivalence of the studied drugs, which indicate about scientifically based approach to the selection of excipients and technological process in the development of the above generic drugs.

Keywords: Non-steroid anti-inflammatory drugs, meloxicam, Dissolution test, bioequivalence.

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Introduction

Meloxicam (Movalis) is a nonsteroid anti-inflammatory drug of the last generation of COX-2 selective inhibitors. Recently meloxicam has become widely used in clinical practice due to better safety profile than conventional NSAIDs.

Studies show similar efficacy but greater safety of meloxicam in compared with diclofenac, piroxicam, naproxen in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis: adverse effects for the digestive tract when taking meloxicam were observed 2.4, 4 and 8 times less, respectively. The reliable data on meloxicam efficacy were obtained in the controlled multicenter comparative study of meloxicam (Meloxicam Large-scale International Study Safety Assessment - MELISSA) at a dose of 7.5 mg/day and diclofenac 100 mg per day. At the same clinical efficacy the rate of gastroenterological side effects while taking meloxicam made 1.8%, and the “standard” NSAIDs - 3.2%. Severe complications were detected in 0.1% and 0.7% respectively. Reducing the risk of side effects while maintaining the clinical effect of meloxicam suggests meloxicam as one of the most promising drugs (Shoenfeld, 1999; Tsvetkova, 2001; Shostak and Shemetov, 2001).

As it is known, drugs with proven bioequivalence are reliable and inexpensive alternative drugs-brands and provide treatment required for all (Meshkovskii, 2003; Belousov, 2003; Panyushin, 2003). Multisource medicinal products, as well as original formulations, must meet all normative and technical requirements and should be bioequivalent. Until recently, this parameter was determined only in experiments in vivo; however, in recent years in vitro dissolution test has become one of the main methods for bioequivalence testing which is considered as to be main method for evaluation of the quality of generic formulations in many countries of the European Community, USA and others (DH RF, 2005).

The present study was undertaken to perform comparative analysis of bioequivalence of tablets and capsules of meloxicam, developed at the Tashkent Pharmaceutical Institute.

Materials and methods

We studied tableted and encapsulated dosage forms of meloxicam. As a reference drug there was used drug-brand - tablets “Melbek”.

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Study of bioequivalence was performed using the in vitro test “Dissolution”. In vitro dissolution test for analyzed formulations of meloxicam was performed according to techniques described in the technical documentation for brand product. The experiments were performed under the following conditions: dissolution medium - phosphate-buffered saline with pH 7.5, the volume of dissolution medium - 500 ml, temperature - 37 ± 10°C, device rotational speed - 150 rev/min.

In these examinations five time points were used instead of a single one. The concentration of active ingredient dissolved into the medium was determined in samples of medium selected at 5, 15, 30, 45 and 60 minutes after the start of the experiment. Studies were performed on 12 samples for each analyzed preparation.

The data obtained were subjected to statistical analysis using the “Microsoft Office Excel 2003”.

To determine the bioequivalence of meloxicam formulations the factors of convergence and difference were calculated. The methodology used is approved by Center for Drug Evaluation and Research and the Human Medicines Evaluation Unit of The European Agency for the Evaluation of Medicinal Products (NIHS, 2000; EMEA, 2001; FDA, 2003).

Difference factor (\( f_1 \)) showing the percentage of difference between the two curves for dissolution time points was calculated as follows:

\[
f_1 = \frac{\sum |R_j - T_j|}{\sum R_j} \times 100
\]

Where \( n \) - is a number of time points; \( R_j \) - is a percentage content of the active ingredient dissolved from standard sample into dissolution medium in the definite time; \( T_j \) - is a percentage content of the active ingredient dissolved from the investigated sample into dissolution medium in the definite time.

Convergence factor (\( f_2 \)) is the logarithm of the sum of squared errors, calculated as the difference between standard and test samples at all time points, calculated as follows:

\[
f_2 = 50 \times \log \left( 1 + \frac{1}{n} \sum \left| R_j - T_j \right|^2 \right)^{-0.5} \times 100
\]

**Results and discussion**

According to data obtained 5 min before the onset the experiment into the medium of dissolution the active ingredients were dissolved: from tablets “Melbek” - 29.1±2.2%, from meloxicam tablets 25.3±2.4%, from meloxicam capsules - 18.0±3.4%. These findings were almost equal at the 30th minute of the experiment and accounted for 74.3±3.7%, 73.1±2.7% and 72.5±2.9%, respectively. By the end of the trials the active ingredient was dissolved from tablets “Melbek” 92.2±3.3%, and from the tableted and the encapsulated forms of meloxicam 94.5±3.0% and 93.7±2.5%, respectively.

In the next stage we calculated the factors of convergence and difference.

In our studies the convergence factor in the bioequivalence testing of the drug-brand and meloxicam tablets was 76, while in the case of comparison between the brand and the meloxicam capsules the index was 52. These findings correspond to the requirements of the FDA and EMEA, according to which the evaluated factor should be in the range from 50 to 100.
A factor of difference, which should be in the range from 0 to 15, in the case of evaluation of bioequivalence of the drug-brand and meloxicam tablets was equal to 4.3; this indicator for the drug-brand and meloxicam capsules was 11.3.

The comparative results of the equivalence of analyzed drugs are given in Table 1.

### Table 1. Findings of Convergence and Difference Factors for Meloxicam Drugs

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Data for tablets “Melbek” and meloxicam tablets</th>
<th>Data for tablets “Melbek” and meloxicam capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean values of number of active ingredient dissolved into the medium, %</td>
<td>Mean values of number of active ingredient dissolved into the medium, %</td>
</tr>
<tr>
<td></td>
<td>Values of the factors</td>
<td>Values of the factors</td>
</tr>
<tr>
<td>Tablets “Melbek”</td>
<td>Meloxicam tablets</td>
<td>Convergence factor</td>
</tr>
<tr>
<td>5</td>
<td>29.1±2.2</td>
<td>25.3±2.4</td>
</tr>
<tr>
<td>15</td>
<td>54.3±2.8</td>
<td>49.8±3.3</td>
</tr>
<tr>
<td>30</td>
<td>74.3±3.7</td>
<td>73.1±2.7</td>
</tr>
<tr>
<td>45</td>
<td>83.9±3.1</td>
<td>84.8±2.8</td>
</tr>
</tbody>
</table>

**Conclusion**

The results of bioequivalence study of meloxicam drugs using in vitro test “Dissolution”, confirm the presence of bioequivalence between the analyzed drugs, which is a direct proof of the scientific basis for selection of excipients and technological process in the development of generic drugs.

**References**


