USE OF THE “DISSOLUTION” TEST FOR EVALUATION OF THE PHARMACEUTICAL EQUIVALENCE OF TABLET FORMULATIONS OF PHENAZEPAM

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Original article submitted March 9, 2006.

Studies of the dissolution of tablet medicinal formulations of phenazepam are reported. The dissolution profiles of these medicinal forms are compared. Comparative evaluation of their pharmaceutical equivalence is presented.

The introduction of stricter specifications for the quality of tablet preparations leads to the urgent need for a constant search for active ingredients of the required quality, more effective and multifunctional accessory ingredients, and the introduction of contemporary technologies and apparatus into drug production. Qualitative and quantitative changes in the composition of accessory substances in medicinal formulations can significantly alter the solubility, dissolution kinetics, and bioavailability of drugs, resulting in changes to the blood concentration and duration of action [1].

One of the major requirements for therapeutic agents when changes are introduced in the composition of accessory substances is to confirm bioavailability and bioequivalence [2]. An alternative to studies of the bioequivalence of different compositions of an agent and a reference preparation is provided by in vitro studies of dissolution, which can provide evidence for similarities and differences between medicinal formulations [2–4]. In this situation, the standard is not the original medicinal formulation, but a series of agents produced before the introduction of changes and tested for bioavailability and bioequivalence to the original preparation [5].

The aim of the present work was to perform comparative assessments of the pharmaceutical equivalence (in terms of dissolution profiles) of medicinal forms of the psychotropic therapeutic agent phenazepam [6], using tablets prepared using the standard technology (1), tablets with an altered accessory substance composition (3), and tablets with a composition analogous to that of tablets (3) but made using ground substance (2).

EXPERIMENTAL SECTION

Study materials. Phenazepam tablets (0.001 g), three versions, corresponding to the specifications of active Manufacturers’ Pharmacopeia Articles (except for qualitative composition).

Test method. Dissolution tests were performed as described in the Manufacturer’s Pharmacopeia Article for “Phenazepam tablets 1 mg”, though several sampling time points were used instead of one.

Tests were performed using a SOTAX AT 7 Smart (Switzerland) instrument and a “Rotating basket” apparatus, with a rotation rate of 100 rpm. Dissolution medium was 0.1 M hydrochloric acid at a volume of 500 ml and a temperature of 37°C.

Tests were performed on 12 tablets of each preparation. Samples were collected at 5, 10, 15, 20, 25, 30, 35, 40, and 45 min after the test started. Samples were of volume 10 ml; volumes were replaced with dissolution medium after sample collection. Samples were filtered through 0.45-μm Millipore membrane filters.

Levels of active ingredient released into the dissolution medium were estimated by UV spectrophotometry in terms of the absorption intensity of the test solutions. Optical densities were measured using a Lambda EZ201 spectrophotometer (Perkin Elmer, USA) in a cuvette with a 10-mm path length at a peak absorption wavelength of 243

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nm with reference to a solution of the working standard sample (WSS) of phenazepam.

At each time point, the proportion of released therapeutic substance (TS), phenazepam, was calculated on the basis of the level in the dissolution medium.

RESULTS AND DISCUSSION

The equivalence of the dissolution kinetics was assessed in accord with the Methodological Specifications of the Ministry of Health and Social Development of the Russian Federation for Studies of the Kinetics of TS Dissolution, in which the stated requirements are for consideration of only one of the calculated mean values of the quantity of released substance for each sample of greater than 85% and for assessment of the standard deviation of each mean value which, with the exception of the first time point, must be no greater than 10% [7].

Figure 1 presents averaged dissolution profiles for phenazepam.

The equivalence of the dissolution kinetics of the TS studied here was assessed in terms of the coefficient of difference and the coefficient of similarity, which were evaluated using the method of the Center for Drug Evaluation and Research (FDA) and the Human Medicines Evaluation Unit of the European Agency for the Evaluation of Medicinal Products (EMEA) [2].

The coefficient of difference ($f_1$) shows the percentage error between the two curves at all time points and is calculated using:

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100, \quad (1)$$

where $n$ is the number of time points; $R_j$ and $T_j$ is the percentages of therapeutic agents released into the dissolution medium at time point $j$.

The coefficient of difference is zero when the profiles of the test and standard TS are identical. The value of the coefficient increases with increases in the difference between the two dissolution profiles.

The coefficient of similarity ($f_2$) is the logarithmic transform of the sum of the squares of the errors calculated from the difference between the test $T_j$ and the standard ($R_j$) samples at all time points. The coefficient of similarity is determined using:

$$f_2 = 50 \times \log \left\{ \left[ 1 + \frac{1}{n} \sum_{j=1}^{n} |R_j - T_j|^2 \right]^{-0.5} \right\}, \quad (2)$$

where $n$ is the number of time points; $R_j$ and $T_j$ are the percentages of therapeutic substances released into the dissolution medium at time point $j$.

The coefficient of similarity can have values ranging from 0 to 100. As the equivalence of the dissolution profiles decreases, the value of the coefficient of similarity approaches zero.

TABLE 1. Comparison of the Equivalence of Dissolution Profiles of 1-mg Phenazepam Tablets and Tablets Prepared by Direct Compression of Ground Substance.

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Concentration of therapeutic agent released into dissolution medium, $C$ (%)</th>
<th>Standard deviation from mean, %</th>
<th>Coefficients</th>
<th>Similar</th>
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<tbody>
<tr>
<td></td>
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<td>test sample tablets (2)</td>
<td>1-mg phenazepam tablets</td>
<td>test sample tablets (2)</td>
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<tr>
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