Dissolution testing has emerged in the pharmaceutical field as a very important tool to characterize drug product performance, for example, to demonstrate similarity between different formulations of an active substance and the reference medicinal product. Moreover, when an *in vitro*/*in vivo* correlation is available, dissolution can be used as a test to reflect the bioavailability of a product in human and therefore, to determine the actual bioequivalence of different products containing the same drug at the same dosage.

Theophylline is a xanthine derivative used in the treatment of asthma. The drug is completely absorbed after the oral administration. Due to its short half-life (3–8 h), it may be necessary to administer an immediate-release formulation several times per day. Therefore, extended-release dosage forms are used to optimize a therapy and patient compliance. The main concern with modified-release formulations is the substitution of one product for another. Because the rate of release of theophylline could differ between the products, the patient health may be endangered, especially that this drug has a narrow therapeutic range.

The aim of study was to compare the dissolution profiles of theophylline extended-release dosage forms available on Polish market:

### EXPERIMENTAL

Pure theophylline was obtained from Sigma Aldrich. Theophylline extended-release dosage forms available on Polish market: Theoplus (Pierre Fabre), Theovent (Glaxo Smith Kline), Theospirex retard (Biofarm), and Euphyllin long (Byk Gulden), all containing 300 mg of theophylline, were used in the experiment.

The release of theophylline from tablets was performed by the basket apparatus type DT700 (Erweka). The dissolution media (1000 mL) were 0.1 M hydrochloric acid (pH 1.2) for the first 2 h and phosphate buffer (pH 7.5) for the next 8 h. The temperature of the dissolution media was maintained at 37 ± 0.5°C, and the basket rotation speed was 75 rpm. A 2 mL sample of the dissolution fluid was collected at 1st, 2nd, 3rd, 4th, 6th and 10th hour of experiment. The samples were analyzed at λ = 271 nm using a HP 8452A (Hewlett Packard) spectrophotometer.

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero-order, first-order (1), Higuchi model (2), and Hixson-Crowell release equation (3), while release mechanism was evaluated by the Korsmeyer-Peppas model (4). The f1 (dif-
Comparison of dissolution profiles of theophylline extended-release dosage forms

ference factor) and $f_2$ (similarity factor) were used to compare the obtained dissolution profiles. Euphyllin long 300 was a reference product and calculations were performed according to FDA guidelines.

RESULTS

The dissolution profiles of the formulations are showed in Figure 1. The value of $f_1$ was 96.52, 21.80 and 35.21 for Theoplus, Theovent and Theospirex retard, respectively, whereas the $f_2$ value was 26.56 (Theoplus), 38.63 (Theovent) and 24.03 (Theospirex retard). The obtained values showed that dissolution profiles are not equivalent to each other. The tablets differed by the mechanism of drug release also. Fickian diffusion for Theovent ($n = 0.325$) was observed, whereas non-Fickian or anomalous diffusion was observed for Theoplus, Euphyllin long and Theospirex retard ($n = 0.841, n = 0.624$ and $n = 0.580$, respectively). The $n$ value for Theoplus suggests that mean drug release does not change over time and the drug is released by zero-order mechanism, what is consistent with its profile of release (Fig. 1). These observation was confirmed by the high value of regression correlation coefficient ($r^2 = 0.992$) (Tab. 1). Release kinetics of Euphyllin long, Theospirex retard and Theovent was consistent with the Higuchi model.

DISCUSSION AND CONCLUSION

Theophylline has a narrow therapeutic range; therefore much attention should be paid to its con-

Table 1. In vitro kinetic values of theophylline release from Theoplus 300, Theovent 300, Theospirex retard 300 tablets and Euphyllin long 300 capsules.

<table>
<thead>
<tr>
<th>Kinetics models</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi</th>
<th>Hixson-Crowell</th>
<th>Peppas-Korsmeyer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r^2$</td>
<td>$K_0$</td>
<td>$t^1$</td>
<td>$K_1$</td>
<td>$t^2$</td>
</tr>
<tr>
<td>Theoplus</td>
<td>0.992</td>
<td>23.82</td>
<td>0.907</td>
<td>0.201</td>
<td>0.912</td>
</tr>
<tr>
<td>Theovent</td>
<td>0.530</td>
<td>21.79</td>
<td>0.442</td>
<td>0.062</td>
<td>0.817</td>
</tr>
<tr>
<td>Euphyllin long</td>
<td>0.819</td>
<td>27.02</td>
<td>0.670</td>
<td>0.132</td>
<td>0.964</td>
</tr>
<tr>
<td>Theospirex retard</td>
<td>0.896</td>
<td>13.46</td>
<td>0.805</td>
<td>0.131</td>
<td>0.995</td>
</tr>
</tbody>
</table>

$K_0$ [mg $\times$ h$^{-1}$] – zero-order rate constant, $K_1$ [h$^{-1}$] – first-order rate constant, $K_H$ [mg $\times$ h$^{-1/2}$] – Higuchi rate constant, $K_{HC}$ [h$^{-1}$] – Hixson-Crowell rate constant, $K_{KP}$ [h$^{-n}$] – Korsmeyer-Peppas rate constant, $n$ – diffusion exponent, $r^2$ – regression correlation coefficient.
centration in plasma. One of the factors affecting the concentration of this xanthine in the blood stream is a rate of drug dissolution. Extended release drugs form should release the active compound with a proper speed to ensure that the concentration of drug is in the therapeutic range. Therefore, the dissolution testing is indispensable.

Differences between the dissolution profiles observed in the present study were probably caused by different composition of the drug formulations. The dissolution of Euphyllin long was significantly faster than from Thoplus and Theospirex what is consistent with the findings of Słodownik et al. (5, 6). They showed that the liberation of theophylline from a gelatin capsules was significantly faster then from a hypromellose (HPMC) capsules.

Gowda et al. (7) stated that Eudragit significantly slowed down the dissolution, however, in the present study, theophylline was the most readily liberated from Eudragit containing preparation – Theovent.

The release of theophylline from the investigated dosage forms differed from each other. Therefore, caution should be exercised when these formulations are used alternatively, especially that theophylline has a narrow therapeutic range.

REFERENCES