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METHODS

The in vitro performance of metronidazole drug products marketed in different countries of the Americas was compared to the US comparator pharmaceutical product (CPP) to determine if they met in vitro bioequivalence criteria.

Disintegration test

The test was performed according to USP general chapter <701>. Disintegration time was measured in a disintegration tester (Eureka, Germany) using 900 mL of phosphate buffer pH 6.8, ± 0.01 ml. Six tablets of each drug product were tested.

Dissolution test

Five commercial metronidazole tablets were tested in compendial Simulated Intestinal Fluid (SIF), as well as in physiological buffer capacity (5mM phosphate buffer at pH 6.8, ± 0.01 mL). The tablets were also tested in a biphasic dissolution system in which the aqueous layer was composed of 200 mL of 5 mM phosphate buffer (pH 6.8) with 100 mL of n-octanol on top.

RESULTS

Table 1. Disintegration time of different commercially available metronidazole IR tablets

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>DISINTEGRATION</th>
</tr>
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<tbody>
<tr>
<td>FLAGYL-USP (CPP)</td>
<td>5.32 ± 0.43</td>
</tr>
<tr>
<td>FLAGYL-MEXICO</td>
<td>18.27 ± 0.58</td>
</tr>
<tr>
<td>FLAGENASE</td>
<td>10.16 ± 0.07</td>
</tr>
<tr>
<td>COLPOFILIN</td>
<td>0.60 ± 0.22</td>
</tr>
<tr>
<td>METRAL</td>
<td>13.32 ± 0.78</td>
</tr>
</tbody>
</table>

None of the tested metronidazole products were in vitro equivalent to the CPP or to other manufacturers in compendial buffer. The tested metronidazole products followed a similar pattern than that obtained in the compendial buffer in the aqueous phase of the biphasic system.

CONCLUSIONS

- None of the tested metronidazole products demonstrated in vitro equivalence to the CPP in the monophasic dissolution methods, i.e. SIF and physiological buffer capacity.
- The monophasic aqueous systems seem to be overdiscriminating.
- The correlation of the organic phase of the biphasic system showed a similar partitioning pattern for all the generic drug products and CPP, which could indicate in vitro equivalence.
- The application of biphasic dissolution to highly soluble drug formulations has beneficial attributes to estimate the in vivo behavior and performance.
- Further in vitro studies with other products are needed to confirm and refine these findings.

REFERENCES AND ACKNOWLEDGEMENTS

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