Deficiency in discriminatory effect of USP-34 dissolution monograph on immediate release Fenofibrate tablets having different particle sizes

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INTRODUCTION
The goal of dissolution testing is to assure the quality of the pharmaceutical products including IR and MR dosage forms and ability to design, evaluate, alter and manufacture in a reproducible manner, maintain stability and meet the product’s biopharmaceutical characteristics throughout the product shelf life. Based on the Biopharmaceutics Classification System (BCS), it is essential to develop dissolution testing conditions that can assess rate and full extent of drug release in vitro and point toward how the product will perform in vivo to support bioavailability and bioequivalence from regulatory point of view and help in establishing relevant IVIVC as shown in Figure 1 [1,2].

RESULTS AND DISCUSSIONS
Table 1 lists the saturation solubility of fenofibrate in different SLS media. Solubility of fenofibrate was linearly increased from 0.8 µg/ml to 910.8 µg/ml as the concentration of SLS increases from 0 to 0.1 M (Figure 2).

<table>
<thead>
<tr>
<th>Medium</th>
<th>Saturation Solubility (µg/ml)</th>
<th>C/C0* (80mg tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deionized Water</td>
<td>0.8</td>
<td>0.01</td>
</tr>
<tr>
<td>0.025M SLS</td>
<td>195.3</td>
<td>2.44</td>
</tr>
<tr>
<td>0.05M SLS</td>
<td>445.9</td>
<td>5.57</td>
</tr>
<tr>
<td>0.075M SLS</td>
<td>728.1</td>
<td>9.10</td>
</tr>
<tr>
<td>0.1M SLS</td>
<td>910.8</td>
<td>11.38</td>
</tr>
</tbody>
</table>

*C0: saturation solubility of fenofibrate; C, concentration of fenofibrate after complete dissolution of tablet (containing 80mg fenofibrate) in 100ml dissolution medium. 

Figure 1. Compendial dissolution apparatus and methods should be used as a first approach in development of IR and MR dosage forms with defined conditions of testing (i.e. Apparatus type, hydrodynamics, pH, type of buffers, ionic strength, surface tension, media volume, biorelevant media, etc.).

Figure 2. Saturation solubility of fenofibrate as a function of SLS concentration.[3]

Figure 3 shows the size analysis result of fenofibrate with different particle size in different media. The resultant particles in the medium are smaller compared to the actual sieve sizes used in sieving analysis, which might be due to the solubilizing effect of SLS.

Figure 3. Size analysis of fenofibrate in deionized water and 0.05M SLS.

Dissolution study: Dissolution testing was performed in accordance with USP 34 monograph for dissolution of IR tablets. Dissolution data for three identical formulations containing different particle sizes of drug show lack of discriminatory power of the dissolution method described in the USP-34 monograph with inconsistency in similarity factor (12) value when dissolution profiles were compared against formulation having particle size >250µm. Results are shown in Figure 4.

Figure 4. Dissolution profiles of fenofibrate IR tablets with different particle sizes in 1000 ml deionized water and 0.05 M SLS solution at 75 rpm, USP-34, Apparatus-II.

CONCLUSIONS
- The media compositions have been shown to influence dissolution rates, extent, or variability in dissolution.
- The data indicates that the high concentration of SLS (0.05M) stated in the Monograph is a poor choice and tends to mask actual differences that may exist among formulations having different drug particle sizes. Monograph in this case may not be discriminatory enough especially when bioequivalence is concerned.
- These findings may have implications as far as bioavailability, bioequivalence, development of IVIVC and therapeutic equivalence is concerned.

REFERENCE

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