Correlation between microstructure and bioequivalence in Anti-HIV Drug Efavirenz

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Efavirenz

- Crystalline solid
- Lipophilic
- BCS Class II
- Polimorph I is commonly used for drug formulation
- Oral bioavailability of 40 – 45%
- In the HAART - the best choice - treatment of adults and children

Figure 1. Chemical structure of EFV. (Adapted from SATEESHKUMAR et al., 2009).
Figure 2. (A) XRPD, DSC-TG and FT-IR of EFV polymorph 1. (B) SEM micrographs of EFV raw material batches 1 – 6.

<table>
<thead>
<tr>
<th>EFV raw material batch</th>
<th>Average particle size d[4, 3] (µm)</th>
<th>Average particle size d[3, 2] (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (bioequivalent)</td>
<td>2.6</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>5.2</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>4.4</td>
<td>2.3</td>
</tr>
<tr>
<td>4</td>
<td>4.4</td>
<td>2.0</td>
</tr>
<tr>
<td>5 (non-bioequivalent)</td>
<td>4.0</td>
<td>2.2</td>
</tr>
<tr>
<td>6</td>
<td>8.8</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Figure 3. Particle size analysis of the six batches of EFV.
Bioequivalence and Dissolution Properties

Figure 4. A) Powder dissolution profile in SLS 0.25% versus time. B) Dissolution Efficiency of six EFV batches of raw materials. Batch 1 passed the bioequivalence test, whereas batch 5 did not.
Two bio-batches, 1 and 5, with the acceptable solid state characteristics and formulations for in vivo studies

Why?

Batch 1 bioequivalent
Batch 5 Non-bioequivalent
**Microstructure in drugs**

- **Raw material**

- **Particle Size / Morphology**
  - 5 – 30 µm

- **Microstructure**
  - 20 – 500 nm

- **Polymorphism**
  - Unit cell
  - 4 – 100 Å

- **Micronized particle**
  - $10^{-6}$ m

- **Crystalline domain**
  - $10^{-8} - 10^{-9}$ m

- **Atoms / Molecules**
  - $10^{-10}$ m
Figure 5. Crystalline microstructure representation (crystallite).
Results

Microstructure – X-Ray Diffraction Pattern

Figure 7. (A) Schematic definition of particle, cluster and crystalline domain (crystallite) size. (B) Example of the XRPD data analysis by the WPPM approach (EFV batch 5): data (circle), model (line) and their difference, or residual (line below).
Figure 6. Crystalline domain size distribution for the six EFV batches of this study.
**Results**

**Dissolution Efficiency vs Particle Size Distribution**

![Graphs showing dissolution efficiency vs average particle size for six batches of EFV raw materials. Batch 1 passed the bioequivalence test, whereas batch 5 did not.](image)

**Figure 8.** DE versus average particle size, and DE versus average crystalline domain size, for six batches of EFV raw materials. Batch 1 passed the bioequivalence test, whereas batch 5 did not. (A) DE versus average particle size $d[4, 3]$. (B) DE versus average particle size $d[3, 2]$. 
Results

Dissolution Efficiency vs Crystalline Domain Size Distribution

Figure 9. DE versus average crystalline domain size $<D>$ (nm).
Results

Bioequivalence / Dissolution Properties $\times$ Crystalline Domain and Particle Sizes

Figure 10. Synoptic 3D view of the relationship among average crystalline domain size, average particle size and dissolution efficiency.
Conclusion

1-Biorrelevance of Microstructure
   - Crystalline domains sizes (Microstructure)
     Batch 1 - 30 nm  Bioequivalent
     Batch 5 - 208 nm  Non – Bioequivalent

2-Solid State Quality Control Parameters (low soluble drugs)
   - Polymorphism
   - Particle size distribution and morphology
   - Crystalline domain size distribution (Microstructure)
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