Pharmacokinetics of fenofibrate nanoparticles stabilized and delivered using the Zydis® Technology

OBJECTIVES
To evaluate the pharmacokinetic (PK) behavior of nanosized fenofibrate administered orally in a stabilized freeze-dried dosage form. The pharmacokinetics of three dosage forms were investigated:
- aqueous nanosuspension (F1),
- nanosized fenofibrate in freeze-dried tablet (F2),
- micron-sized fenofibrate in freeze-dried tablet (F3).

METHODOLOGY
Fenofibrate is a poorly soluble drug that is orally administered to treat hypercholesterolemia. The brand product Tricor® is formulated using the Nanocrystal™ Technology.

Nanosuspension was prepared by media milling fenofibrate suspended in aqueous solution containing dissolved gelatin and mannitol.

Freeze-dried tablets were manufactured using the Zydis® Technology directly from the nanosuspension to form a unit dose of 48 mg. See Figure 1 for process schematic. No additional excipients were added to the formula to support a stable freeze-dried tablet. Freeze-dried tablets were also made from a micron-sized fenofibrate suspension to provide a non-nanosized reference test article. For in vivo testing, six beagle dogs were administered 48 mg fenofibrate in the fasted state. Bioanalysis was performed using a validated LCMS method measuring the active metabolite fenofibric acid.

RESULTS
Nanosized fenofibrate was stabilized in the freeze-dried matrix prepared using the Zydis Technology. Due to the high water-solubility of the matrix-forming excipients, particle size of suspended API is easily measured using laser light diffraction. Particle size was measured for the nanosuspensate fenofibrate Zydis tablet by laser light diffraction using water dispersant. A size of 165 nm was measured (see Figure 2 for size distribution and reference products).

In vitro dissolution testing of the freeze-dried tablet containing nanosuspensate exhibited >90% dissolved drug after 5 minutes (Figure 3). PK studies yielded tmax results of 0.83 (F1), 1.08 (F2) and 9.08 hours (F3), demonstrating that nanosized API in a freeze-dried tablet disperses rapidly in vivo to provide a rate of absorption comparable to a nanosuspension. AUC values were 33739 (F1), 25749 (F2), and 13502 (F3), showing that the freeze-dried tablet with nanosized API increases bioavailability versus a micron-sized reference tablet, but does not match the exposure provided by the reference nanosuspension.

<table>
<thead>
<tr>
<th>Formula</th>
<th>tmax (min)</th>
<th>cmax (ng/ml)</th>
<th>AUC (ng*hr/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.83</td>
<td>4777</td>
<td>33739</td>
</tr>
<tr>
<td>F2</td>
<td>1.08</td>
<td>4397</td>
<td>25749</td>
</tr>
<tr>
<td>F3</td>
<td>9.08</td>
<td>1449</td>
<td>13502</td>
</tr>
</tbody>
</table>

Table 1: Pharmacokinetic parameters for three fenofibrate dosage forms

CONCLUSIONS
Nanosuspensions were successfully stabilized and delivered orally using freeze-dried tablets. The rapid in vitro dissolution rate of nanoparticulate fenofibrate in a freeze-dried tablet translated to rapid in vivo absorption and short tmax. The reduction in particle size to the nano range improved oral bioavailability, but was not equivalent to nanosuspension.