Enhancement of solubility and Bioavailability of a poorly water-soluble drug by Solid dispersion technique
Sumit Patil, C. Pradeep Kumar Reddy, R. Manikandan, Krishnakant T. Gandhi
Dr. Reddy’s Laboratories Limited, Hyderabad, Andhra Pradesh, 500070, India.
sumitpatil@drreddys.com

ABSTRACT
With the advent of combinatorial chemistry and high throughput screening in drug discovery, number of poorly water soluble compounds has considerably increased and this type of compounds poses challenge in meeting dissolution and bioequivalence while developing generic dosage forms. In the present study, solid dispersion technology was used to design generic dosage form, where the hydrophobic drug was dispersed in hydrophilic matrix to improve the solubility and to meet bioequivalence. The developed solid dispersion was in amorphous form and found to be stable under accelerated storage conditions. The tablet dosage form designed as amorphous solid dispersion (DRL109B) was bioequivalent with reference product (DRL109R) in fasting bioequivalence studies.

INTRODUCTION
The improvement in solubility behavior and to meet bioequivalence for BCS class IV drugs remains as one of the major challenge in formulation development. Different techniques such as reduction in particle size, modifications of the crystal habit, Polymorphs, (Pseudo polymorphs, including solvates), Complexation/ solubilization have been explored where each method has its own pros, cons and scalable issues. There are many reported literature, which states that solid dispersion is one of promising technique to improve solubility and to meet bioequivalence. Based on this understanding, solid dispersion technology was adapted to improve solubility, dissolution and to achieve bioequivalence with reference product for DRL109B.

EXPERIMENTAL METHODS
Two formulations were prepared one with conventional method (DRL109A) and other with solid dispersion technique (DRL109B). In formulation DRL109A, drug was added in dry mix of lactose monohydrate and crospovidone. This mixture granulated with binder solution containing PVPK30 in water. In formulation DRL-109B API was added in binder solution in 1:10 ratio API: PVP K-30. In both strategy, granules were dried (Fluidized bed dryer), milled (Quadro co-mill) and lubricated with magnesium stearate in double cone blender. Final blend was compressed into tablets using kambert 8 station compression machine and coated with Opadry white 58900 to target of 3% weight gain in Neocota coating machine. API and solid dispersions were characterized for solid state characterization for XRD (Panalytical) & solubility studies using shake flask method. Dissolution studies were performed for prepared formulations in purified water containing 1% polysorbate 20 using electrolab dissolution apparatus and samples were analyzed by validated HPLC method. Two-way crossover fast state bioequivalence study was conducted in 15 healthy volunteers on test formulations (DRL109A & DRL109B) and evaluated for Cmax, AUC and Tmax considering DRL109R as reference product, which is approved by European medicines agency and listed in electronic Medicines Compendium (eMC).

RESULTS AND DISCUSSION
In test formulation 109A, it was observed that drug remains in crystalline form. While in 109B, drug gets converted to amorphous form, where the drug get molecularly dispersed as glass solution confirmed by XRD method (Fig. 1)

Fig. 1 XRD Analysis

Fig. 1a. API
From the solubility studies (Table 1) it was observed that there was improvement in solubility for solid dispersion in ratio 1:10 (API : PVP K-30) compared with API.

**Table 1. Solubility of API and solid dispersion**

<table>
<thead>
<tr>
<th>Media</th>
<th>API (mg/250ml)</th>
<th>Solid Dispersion (mg/250ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1N HCl</td>
<td>0.0375</td>
<td>0.305</td>
</tr>
<tr>
<td>0.001N HCL</td>
<td>0.0325</td>
<td>1.3275</td>
</tr>
<tr>
<td>pH4.5 Acetate</td>
<td>0.0475</td>
<td>2.265</td>
</tr>
<tr>
<td>Water</td>
<td>0.0450</td>
<td>1.3625</td>
</tr>
<tr>
<td>pH6.8 Phosphate</td>
<td>0.5025</td>
<td>2.595</td>
</tr>
<tr>
<td>2.1SGF+0.1% P 20</td>
<td>36.9200</td>
<td>42.35</td>
</tr>
</tbody>
</table>

Formulation DRL109A shows 69% of drug release in 30min compared to DRL109B and DRL109R, 96% & 90% respectively. It was observed that there was improvement in dissolution for solid dispersion formulation compared to conventional formulation.

**CONCLUSION**

It can be concluded, in generic formulation to be bioequivalent with reference product in particular for BCs class-IV molecules, selection of technology becomes critical to prove the product to be pharmaceutically equivalence. The adopted solid dispersion technology can be one of the promising approach for poorly water soluble drugs to meet bioequivalence with marketed formulations. This technology can be easily scalable to commercial scale compared to other techniques reported in literature.

**REFERENCES:**

**ACKNOWLEDGMENTS**

The authors gratefully acknowledge the management of Dr. Reddy’s Laboratories Limited for allowing us to carry out the present work.