Use of Nano-Capsule technology to improve In-Vitro dissolution of Itraconazole

**OBJECTIVE**
To evaluate the use of Nano-capsule technology to improve the in-Vitro dissolution of itraconazole.

**RATIONALE**
Poorly soluble drug molecules are a continued challenge to the Pharmaceutical companies involved in drug development of NCEs. Typical strategies that are often used to aid the development of such molecules include the nano-crystal technique. This involves the reduction of the particle size by milling to produce an increase in surface area and aqueous solubility, dissolution rate and absorption. One alternative strategy used involves the use of lipid and other non-aqueous solvents to produce solutions or suspensions of the drug which can then be filled into hard gelatine capsules. The Nano-Capsule™ technology combines these two approaches and produces nano-crystal suspensions of drugs in liquid fill excipients which are then filled into capsules. Nano-crystals can be formed by wet milling in aqueous media (traditional route) or potentially by milling directly in the lipid or liquid fill excipient prior to filling into capsules. If the traditional wet milling in aqueous media is used, then nano-crystals have to be recovered from the aqueous suspension and dried before further processing.

**METHODS: Milling**
A 15%w/v aqueous suspension of itraconazole containing stabilizers (to prevent aggregation of the nano-particles in liquid form) was processed using the Lena DM100 size reduction mill. The Mill has 150mLs of Yttrium stabilised Zirconium beads (size 0.2mm) as the grinding media. The rotor in the rig rotates at 1400rpm and the processing is recycled for 90minutes. After the production of the nano-suspension, the nano-crystals were recovered from the aqueous media by spray drying with mannitol. Milled API was also recovered from the nano-suspension by Vac drying.

The milling was performed by Lena Nanoceutics using their patented technology. This allows milling to be completed in minutes rather than the days which is common with conventional bead milling processes.

**METHODS: Development and Evaluation of Nano-capsule**
Nano-milled drug (0.6g) was dispersed in 4.0g of each of Vitamin E TPGS and Gelucire 44/14, at 50°C to form a suspension, and filled into gelatin capsules (itraconazole content was 40mg). Comparative capsules containing 40mg of non-milled itraconazole in Vitamin E TPGS and Gelucire 44/14 were also prepared. Dissolution analysis was conducted using USP II apparatus in 0.1N HCl. Samples were removed at various time points, up to 45mins, followed by an infinity spin. Samples were analysed by HPLC to determine the drug dissolution concentration.

**RESULTS AND DISCUSSION**
Nano-milled itraconazole showed an improvement in dissolution concentration when compared to the non-milled drug. Vitamin E TPGS and Gelucire 44/14 nano-milled drug capsules showed greater dissolution concentration compared to the equivalent non-milled drug capsules. In addition, Vitamin E TPGS and Gelucire 44/14 nano-milled capsules showed the highest final dissolution concentration after infinity spin.

Furthermore drying of the Nano-suspension using a vacuum drying process did not affect the observed improvement in dissolution.

**CONCLUSION**
Nano milling of itraconazole in combination with Liquid fill technology has been shown to offer a significant improvement in the in-vitro dissolution characteristics. The excipients reported have been semi-solid matrices at room temperature. Further work is planned to examine the effect of more complex liquid and semi-solid formulations. This combination technology offers a potentially improved route for the delivery of poorly soluble compounds.

**NEXT STEPS**
- Assess stability of capsules filled with nano-milled formulation
- Evaluate milling of API directly in non-aqueous excipients
- Perform PK assessment of formulations to assess In vivo bioavailability

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