Application of PRINT Microparticle and Nanoparticle Technology – Toward Preparation of Ophthalmic Suspension Formulations with Improved Tolerability and Efficacy

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Purpose:
To use PRINT technology, a novel particle engineering approach, to produce micron and nanoparticles of controlled microstructure and nanostructure that are suitable for the preparation of aqueous ophthalmic suspension formulations without use of solubilizing excipients (e.g. cremophor, oils, cyclodextrins).

Methods:
PRINT technology, a novel drug/exipient micromolding approach, was used to produce monodisperse nanospherical particles of itraconazole, cyclosporine, and tacrolimus. Dissolution characteristics of itraconazole suspensions were evaluated and compared to bulk and micronized itraconazole using standard dissolution test methods.

Results:
Monodisperse, shape-specific microparticles and nanoparticles were successfully prepared of cyclosporine, tacrolimus, and itraconazole. Characterization of these particles using scanning electron microscopy confirms that monodisperse populations of particles were produced of cyclosporine, tacrolimus, and itraconazole, respectively. The sizes and shapes of these microparticles and nanoparticles are suitable for use in ophthalmic suspension dosage forms. Dissolution studies of itraconazole cylinder suspensions indicate that these particles dissolve faster under sink conditions than traditional micronized itraconazole (50% dissolution at 5 min for PRINT-itraconazole cylinders vs. 15 minutes for micronized itraconazole), suggesting that itraconazole PRINT formulations may have greater ocular surface bioavailability than traditional micronized formulations.

Abstract

Platform Capabilities for “Hard to Formulate” Small Molecules and Biologics

Benefits of the PRINT Platform for Ocular Drug Delivery

Implants
- Reproducible implant size, dose and cost-effective manufacturing
- New targets for tissue delivery in the eye
- Simple delivery

Micro/Nano Particles
- Topical delivery with fewer doses
- Sustained release
- Targeted drug delivery

Example: Itraconazole Microparticles

PRINT® Technology
- Brings the precision and control of semiconductors to life sciences and other markets
- Proprietary design and manufacturing platform to produce nanoparticles and films
- Monodisperse feature morphology designed into master template
- Readily scalable using proven roll-to-roll manufacturing process

Printer Process. A precise mold having micro- or nanoscale cavities (upper middle) is then filled with drug product and formed into particles (top row, right). Particles can be removed (bottom row, middle) from the mold and isolated as stable dispersions or free flowing powders (bottom row, left).

Dissolution Testing of Itraconazole Particles

Conclusions
- Small molecules, biologics, and polymer microparticles and nanoparticles were formulated with high monodispersity and controlled geometry using PRINT technology
- PRINT process preserves biochemical activity and physical structure of API
- Enhanced dissolution kinetics were observed of microfabricated itraconazole particles, compared to traditional crystalline or microrized forms, which may enhance bioavailability of poorly soluble compounds

Methods
- Itraconazole PRINT particles were fabricated using a proprietary molding process, as previously described (2). Jet-milled itraconazole was prepared using a Glen Mills Laboratory Jet Mill. Particle physical morphology was characterized by scanning electron microscopy.
- Volume median diameter (VMD) was determined by laser diffraction.
- The dissolution profiles were measured using an Itraconazole suspension containing 0.1% w/v polyvinyl alcohol, acting as a wetting agent, and at a final drug concentration of 10 µg/mL. The dissolution medium consisted of 0.1N HCl and 0.3% w/v SDS and was maintained at a stirring speed of 100 RPM, as previously described for the evaluation of itraconazole formulations for pulmonary delivery (1). Sink conditions were maintained throughout.
- Dissolution test samples were removed and filtered using a 0.22 µm PES filter (Millipore) every 5 minutes for 30 minutes, then at 45, 60, 90, 120 and 240 minutes. Itraconazole content was measured using an RP-HPLC isocratic method and Waters Symmetry Shield RP18 column. Mobile phase consisted of 20 mM hexanesulfonic acid and methanol (20:80) and a flow rate of 1 mL/min was used. UV absorbance of itraconazole, with a retention time of 4.5 minutes, was measured at 260 nm.

References