Assigned AAPS Poster Number

R6108

ElectroNanospray™-Produced Amorphous Nanoformulations of Itraconazole with Enhanced Neutral Phase Dissolution Profiles

Robert A. Hoerr, James E. Lasch, Andrew J. Goode, Doua Thao, Cole Batty, Joseph P. Wyman, Huijing Fu

Nanocopoeia LLC, 1246 University Ave W, Saint Paul, MN 55104

Introduction and Research Objectives

Objectives.

- Prepare amorphous, submicron powdered formulations of itraconazole (ITZ), using the single-step ElectroNanospray process and
- Compare the dissolution performance of these formulations in biorelevant media with the innovator formulation used in Sporanox® capsules (Janssen).

Background. Itraconazole (ITZ) is a BCS Class II anti-fungal compound with very low solubility, varying from 1 ng/mL at neutral pH to 4 µg/mL in acidic media (pKa is 3.7). Sporanox capsules show higher solubility at gastric pH, but ITZ concentrations drop rapidly after transition to neutral pH. Due to the limited solubility of ITZ at intestinal pH levels, multiple approaches have been taken to improve its performance, including reducing particle size and converting it into amorphous solid dispersions and using processes like hot melt extrusion (HME), solvent precipitation, and solvent spray drying. Various excipient combinations have been employed with one or more of these processing methods; e.g. amorphous dispersions of ITZ and Eudragit® co-polymers made using HME have achieved supersaturated concentrations in solutions at pH>6.

The ElectroNanospray (ENS) process. The ENS process has been successfully scaled from capillary electrospray to a system that uses an array of multi-cone-jet nozzles. ENS is a single-step process that operates under ambient conditions. Solutions of drug and excipient, when subjected to high voltage, form cone jets that emit microdroplet spray plumes. Due to their high surface area, they flash off solvent rapidly, generating solid dispersions of drug and excipient that consist of **amorphous, submicron particles.** We predicted that if we used ENS to process ITZ with Eudragit E100 and L100-55—the same polymeric excipients used to create amorphous ITZ dispersions with HME, the resulting product should perform as well, and perhaps better, because it would be not only amorphous but also in the form of submicron particles.

Eudragit® E100 and L100-55 are methacrylate-based co-polymers with contrasting pH sensitivity:

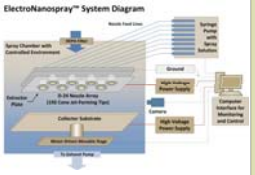
- E100 dissolves at pH<5 and is a cationic copolymer with dimethyl aminoethyl functional groups (R=$COOCH_2$-CH_2-$N(CH_3)_2$-
- L100-55 dissolves at pH>5.5 and is an anionic copolymer with carboxylic acid functional groups (R=-COOH).

In previous studies, we had determined that a 1:2 ratio (w/w) of ITZ with Eudragit performed as well or better in dissolution than a 1:1 ratio or 1:4 ratio, so the studies described here used the 1:2 ratio.

Electrospray system and process

Spray solutions were prepared by dissolving Eudragit E100 or L100-55 polymer in a blend of ethanol and acetone (3:2 v/v). ITZ was first dissolved in dichloromethane and then added to the polymer solution, resulting in a concentration of ITZ at 1% w/v, alone or with E100 or L100-55 at 2% w/v.

Spray solutions to the ENS nozzle array were delivered by syringe pump. Sprayed powder was harvested from a stainless steel plate located 15.25 cm beneath the nozzle array and stored in desiccant until characterization and dissolution testing.



Multi-jet D24 Nozzle

Characterization and Dissolution: Experimental Approach

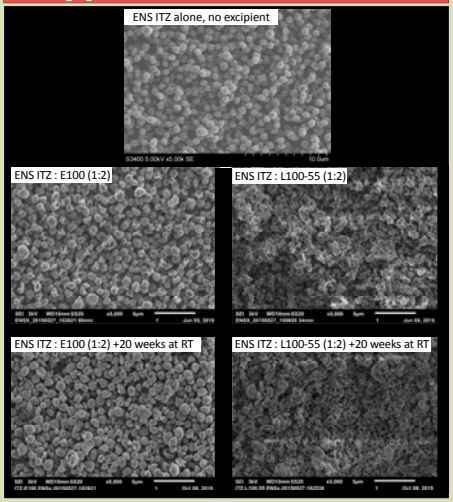
Classical dissolution in Biorelevant media. ENS powders were compared with Sporanox in a 100 mL biorelevant media (n=3 per formulation), using a 100 mL-vessel modified Apparatus 2. Test product was dissolved in FaSSGF, at pH 1.6 and 37°C., sampled for 2 h, transitioned to FaSSIF pH 6.5 using a concentrated transition medium, and sampled for an additional 3 h. Dissolution studies were conducted with product made shortly before the study., while the studies below used ENS powders that had been maintained for 20 weeks at room temperature.

Real-time monitoring of dissolution using the µDISS fiber optic spectroscopy system (pION). Test vessels were filled with 15 mL FaSSGF. Test product providing 1.2 mg ITZ equivalent per cell was added. ITZ concentration was measured for 1 h, then 5 mL transition medium containing buffer and SIF powder (Biorelevant.com) was added, resulting in a transition to FaSSIF. ITZ concentration was measured for an additional 2 h. Media were maintained at 37°C.

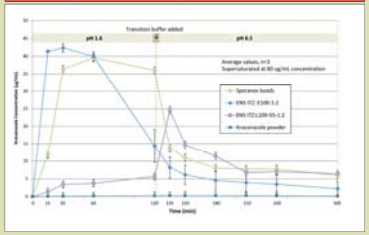
Laser diffraction studies of particle size in biorelevant media. In order to evaluate the physical status of the ENS powders throughout the FaSSGF-to-FaSSIF dissolution study, we conducted companion laser diffraction studies, using a Horiba LA-960 laser diffraction analyzer fitted with a 10 mL sample vessel. Repeated measurements were made during the first 30 min, in FaSSGF, and over a 3 h period following transition to FaSSIF.

XRD analysis of powder sediment during 2-stage dissolution. The physical state of ENS material during the 2-stage dissolution studies was assessed by harvesting particulate matter from test media and obtaining XRD spectra. Test powder was added to FaSSGF and stirred for 30 min, when a 15 mL aliquot was removed and replaced with 15 mL transition medium to FaSSIF. After 30 min in FaSSIF, a final sample was taken. Aliquot were centrifuged at 13,000 rpm. The resulting pellet was transferred to silicon wavers and analyzed by a mini-Rigaku benchtop XRD system.

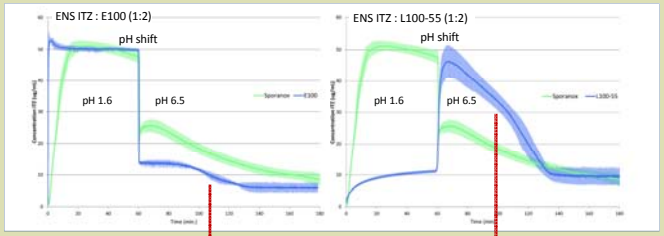
SEM Imaging



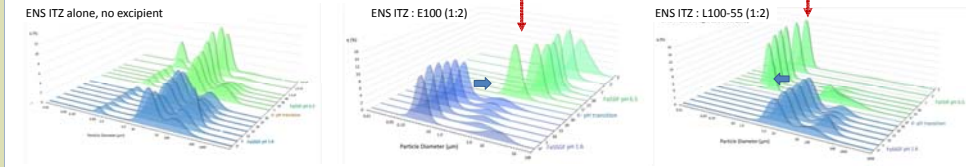
ITZ-Eudragit Powders vs Sporanox® Dissolution



ITZ-Eudragit Powders vs Sporanox® in 2-Stage Biorelevant Media Model: µDiss System by pION



Laser Diffraction Particle Size after Dispersion of ENS ITZ and ITZ-Eudragit Powders in Biorelevant Fluid: Time Sequence Studies



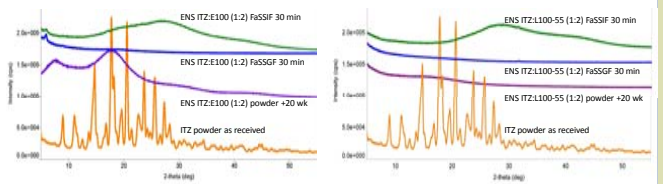
For ENS ITZ without Eudragit, particle size was relatively larger, and there is no size shift when pH increased from 1.6 to 6.5

Note shift in particle size when pH increases from 1.6 to 6.5: ENS ITZ:E100 particles become larger, ITZ:L100-55 particles become smaller

Summary and Conclusions

- Eudragit powders were amorphous by XRD, and remained amorphous after 20 weeks at room temperature.
- ENS processing permitted single-step production of submicron formulations of ITZ and Eudragit E100 and L100-55.
- SEM imaging showed that all ENS powders are submicron particles, though E100 particles were somewhat larger than L100-55 particles.
- In 2-stage dissolution studies using biorelevant media, with FaSSGF (pH 1.6) transitioning to FaSSIF (pH 6.5):
  - For ENS ITZ:E100, ITZ concentrations rose to supersaturated levels rapidly at pH 1.6, but decreased to levels lower than for Sporanox at pH 6.5.
  - For ENS ITZ:L100-55, ITZ concentrations remained low at pH 1.6, but rose to supersaturated levels quickly following the transition to pH 6.5.
- Real-time, *in situ* ITZ concentration measurements in the pION system captured changes during the first 15 min at both pH levels that were missed in the standard USP II-paddle dissolution test. For ENS ITZ:L100-55, ITZ concentrations rose to levels at neutral pH that were attained by Sporanox only in acidic medium.
- Laser diffraction studies showed that the ENS ITZ:L00-55 powder maintained a suspension of submicron particles (190 nm) throughout 3 h in FaSSIF, correlating with the enhanced dissolution at pH 6.5 seen in the dissolution studies, .
- XRD showed minimal conversion to crystalline form in solution, even while free ITZ concentrations fell for E100 material. Formation of cloudy solution with visible white particles after pH transition to 6.5 may reflect polymer agglomeration without crystallization, perhaps with sequestration of ITZ.
- ENS processing, which provides both particle size reduction and amorphous conversion in a single-step, improved dissolution performance of the BCS Class II drug itraconazole at neutral pH levels, when formulated with Eudragit L100-55.

XRD of ENS Powders During Dissolution in FaSSGF (+30 min) and after Transition to FaSSIF (+30 min)



After the pH increase to 6.5, E100 material visibly agglomerated and ITZ concentration fell, yet it remained largely amorphous for at least 30 min

pH 1.6 medium clouded when L100-55 material added; ITZ was amorphous, solubility low; remained amorphous after 30 min at pH 6.5.

References

[1] Miller DA, DiNunzio JC, Yang W, McGinity JW, Williams RO 3rd. Targeted intestinal delivery of supersaturated itraconazole for improved oral absorption. Pharmaceutical Research, 25(2008) 1450-1459