Formulation Development, cGMP Manufacturing and Characterization of a Novel Transdermal Formulation for E/Z-Endoxifen

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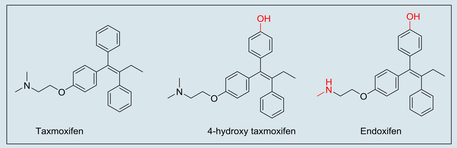
PURPOSE

To develop a pharmaceutically stable, transdermal delivery strategy for endoxifen for use in a prevention breast cancer clinical trial.

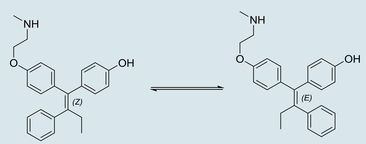
Endoxifen is a selective estrogen receptor modulator (SERM), structurally related to tamoxifen and 4-hydroxytamoxifen.



Breast cancer prevention requires only that the breast be exposed to the drug; systemic exposure is both unnecessary and potentially harmful.

OBJECTIVES

1. A pharmaceutically stable transdermal/topical formulation
   a) Challenge – Endoxifen undergoes facile isomerization. It is important that the drug product not change over the course of the study, therefore either a stabilized form of the Z-isomer is needed since the Z-isomer is the active conformation, or a stable mixture (E/Z) would be required.



2. Clinical trial material for use in Phase I study
   a) Challenge - Material meeting US FDA regulatory requirements was necessary (i.e., material prepared in accordance with Good Manufacturing Practices (GMP) suitable for use in a Phase I trial).
3. Supporting analytical chemistry
   a) Challenge - Appropriately validated stability indicating HPLC methods were required.

METHODS

Formulation

1:1 ratio of E/Z-endoxifen drug substance dissolved in ethanol, adding oleic acid as a permeation enhancer, and then adding phosphate-buffered water. Hydroxypropyl methyl cellulose was then added as a thickening agent to produce the final bulk gel.

Manufacturing

cGMP manufacturing was conducted in the same manner as the developmental batches, albeit using approved batch production records, in accordance with cGMPs. The final product was packaged in amber TopiPump® dispensers set to deliver a metered 1 mL dose per pump.

Analytical

HPLC system was used with UV detection at 243 nm operating under an elution gradient of 40:60, 10 mM HCOONH4 in water, pH 4.3: 10 mM HCOONH4 in MeOH (A) and methanol with 10 mM $HCOONH_4$ (B). The column is a phenyl-hexyl column (3 mM, 150 x 4.6 mm), at 30 °C with a 1.0 ml/min flow over 30 min. Sample concentration is 0.2 mg/mL using a 20 µL injection vol.

RESULTS

Formulation

- Solubility studies showed endoxifen was soluble in ethanol but only had limited water solubility; therefore a balance between EtOH:buffer ratio was needed
- Z-endoxifen isomerizes readily under a variety of conditions explored for topical dosage preparation (e.g., ethanol, ethanol/buffer) – see Figure 1
- A formulation of purified Z-endoxifen in ethanol/phosphate buffer (~1:1 ratio of ethanol:buffer) was also unstable – see Figure 2
- By equilibrating Z-endoxifen into ~ 1:1 E/Z-endoxifen, it provided a stable option for formulation. This material appeared stable in various dosage strengths (e.g. 0.5%, 1.0%)
- It was noted that a 2.0% formulation could not be achieved due to the product precipitating out of solution after ~30 days

Analytical

- Analytical method was developed based on a current method for Z-endoxifen and showed excellent resolution between the E- and Z-isomers
- Validation was conducted in accordance with cGMPs and ICH guidelines. All protocol specifications were met
- Stability was performed showing the dose formulation was stable over time.

Figure 1. Z to E isomerization in Different Solutions

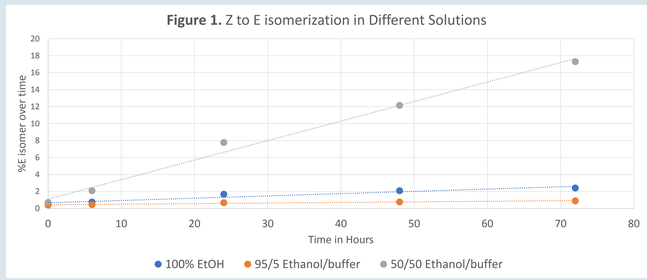
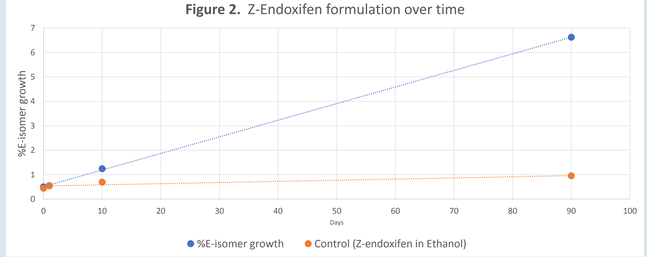
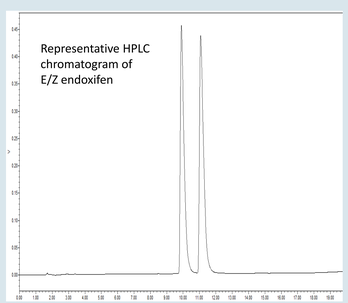
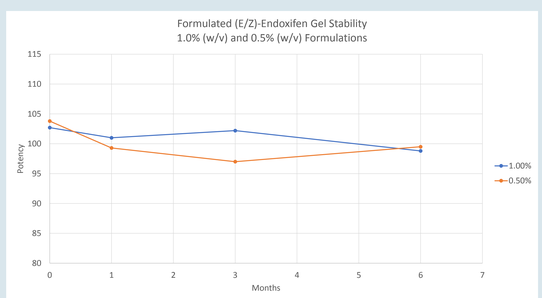


Figure 2. Z-Endoxifen formulation over time







RESULTS

cGMP Manufacturing

- Manufacturing was performed in accordance with US FDA regulations for Phase I cGMP materials
- The bulk drug product was produced on ~5 kg scale for each placebo, 0.5% and 1.0%
- Batch homogeneity was confirmed via in-process and final product release testing and in all cases the material met specifications
- Material viscosity was consistent throughout
- Final product was packaged in TopiPump® dispensers for topical application

CONCLUSIONS

- A pharmaceutically stable, topical dosage of E/Z-endoxifen was developed
- 0.5%, 1.0% and placebo were manufactured on ~5 kg bulk drug product scale for each dosage
- Prototype material was analyzed for shelf life stability and found to be stable over a period of six (6) months
- cGMP manufactured material was analyzed and met specifications
- cGMP manufactured material is currently on shelf life stability testing – initial results align with prototype results adding confidence to the stability
- A stability indicating analytical method was developed and validated and is currently in use for release and stability testing

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