Development of Annual Implant for the Controlled Release of Anastrozole using Polyurethane as a Rate Limiting Membrane

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ABSTRACT SUMMARY
This current work outlines the development and initial clinical evaluation of an annual, non-biodegradable, subcutaneous implant that uses an aliphatic polyurethane as a semi-permeable membrane for the controlled pseudo-zero order release of anastrozole, USP.

INTRODUCTION
Polyurethanes (PU) have been used extensively in medical devices, but have not been extensively investigated for their potential controlled release properties. In the delivery system discussed in this paper, aliphatic polyurethane is used as the semi-permeable membrane for the controlled release of the aromatase inhibitor anastrozole.

Polyurethanes are unique in that they are biocompatible, bio-stable, flexible, and strong. Aliphatic polyurethanes consist of a hard and soft segment arrangement where the hard segment does not contain an aromatic ring structure (e.g. methylene diphenyl disocyanate) that could degrade to potentially carcinogenic aromatic anilines.

The mechanism for controlled drug release is thought to be based on the partitioning of the active into the PU followed by diffusion of the active out of the PU and into the sink-like conditions outside of the implant site. The rate controlling variables include the concentration of the active inside the implant, the chemical composition of the PU, the solubility of the active in the polyurethane soft segment, partition of the drug into the PU, the thickness of the PU wall, and the surface area of the implant.

Several different types of PU where explored to provide an implantable controlled release system capable of releasing a physiologically relevant level of anastrozole over a period of up to 12 months. Following the selection of the lead polyurethane type and grade that yielded the best release characteristics, implants were first evaluated in an animal model to determine an experimental in-vitro – in-vivo correlation (IVIVC) and then further evaluated under an approved investigational new drug application for a first in human proof of concept for a non-biodegradable anastrozole subcutaneous implant.

EXPERIMENTAL METHODS
The implants were prepared by combining anastrozole, USP (Figure 1) with GRAS excipients and lubricants. The anastrozole blend was then compressed into 42 mg pellets. To achieve implants with an anastrozole potency of approximately 380 mg, nine pellets were sealed into polyurethane tubes and sterilized by gamma irradiation. Table 1 contains a list of selected polyurethanes, with key thermoelastic properties, evaluated for long-term in-vitro anastrozole release rates.

Figure 1: Anastrozole

Table 1: Select Properties of Polyurethanes

<table>
<thead>
<tr>
<th>Polyurethane Type / Grade</th>
<th>Shore Hardness</th>
<th>Soft to Hard Segment Ratio</th>
</tr>
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<tbody>
<tr>
<td>Carbothane® PC-3575A</td>
<td>71A</td>
<td>High</td>
</tr>
<tr>
<td>Tecoflex® EG-85A</td>
<td>77A</td>
<td>Medium</td>
</tr>
<tr>
<td>Tecoflex® EG-93A</td>
<td>87A</td>
<td>Low</td>
</tr>
</tbody>
</table>

To determine the long-term in-vitro drug release rate, individual implants were placed into a vessel containing a fixed volume of 0.9% saline media. The implant-containing vessels are maintained at 37 °C and agitated at 100 rpm around a 1” orbit. Every 7 days, the implant was removed and placed into a new vessel containing fresh media and the original media was analyzed against the compendial reference standard using a modified procedure based on the Anastrozole USP drug substance method. The anastrozole concentration is normalized for media volume and days under elution, and then graphed to determine the long-term elution rate.

To determine the in-vivo drug release rate, the non-biodegradable implants were recovered from the in-vivo models and assayed for residual anastrozole potency using a modified stability-indicating assay based on the USP Anastrozole drug substance method. The difference between the initial assayed potency and residual potency, normalized for the days implanted, yields the average in-vivo release rate.

RESULTS AND DISCUSSION
Out of several polyurethanes initially evaluated, Carbothane® PC-3575A and Tecoflex® EG-85A yielded long-term drug release rates that demonstrated potential for further development. In consideration of the proposed drug release hypothesis, a correlation of the theoretical soft segment ratio to the drug release rate suggested that a polyurethane material with a lower soft segment percentage would yield a lower initial rate of release and better zero-order release kinetics. As presented in Figure...
2, Tecoflex® EG-93A yielded pseudo zero-order release kinetics in excess of one year.

Figure 2: Anastrozole Subcutaneous Implants Formulated with Tecoflex® EG-93A

Implants manufactured with Tecoflex® EG-93A were evaluated in a pharmacokinetic animal study for an exposure period of 336 days. The implantation occurred after a two-week period in which an oral formulation of anastrozole was administered to the animals to allow for an internal study control and a one-week washout period. As presented in Figure 3, Evaluation of the anastrozole blood levels supported a delivery rate in excess of the trough levels for the oral comparator.

Figure 3: Anastrozole Release from Pre-Clinical Pharmacokinetic Evaluation

Concurrent with this study’s sample implantation period, six control samples were evaluated for in-vitro release rate. By the procedure previously described, an IVIVC of 1.2 for the first in human study was calculated based on an average in-vivo release of 0.549 mg/day and the average in-vitro release of 0.681 mg/day. Table 2 presents the results from the analysis of the recovered in-vivo samples.

Table 2: Human In-Vivo Potency Results

<table>
<thead>
<tr>
<th>(n=10)</th>
<th>Initial Potency (mg)</th>
<th>Residual Potency (mg)</th>
<th>Released (mg)</th>
<th>Duration Implanted (days)</th>
<th>Release Rate (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>384.2</td>
<td>361.7</td>
<td>22.5</td>
<td>41</td>
<td>0.549</td>
</tr>
</tbody>
</table>

Finally, in both the animal pharmacokinetic study and the clinical evaluation, an absence of related compounds above the assay method’s quantitation limit of 0.05%, in both the recovered in-vitro and in-vivo implants, as well as an obtained mass balance of approximately 100% when combining the summed in-vitro release rate and the residual in-vitro potency assay, strongly suggest no significant degradation of anastrozole occurs due to exposure to physiological conditions over extended time periods. In addition, evaluation of these recovered implants yielded no visual irregularities, no detectable degradation to the polyurethane membrane surface, and no significant loss of integrity or tensile strength of the implants.

CONCLUSION

Implants formulated with Tecoflex® EG-93A as a rate-limiting membrane have been shown to deliver therapeutic amounts of anastrozole in both pre-clinical and clinical studies. Evaluation of recovered anastrozole implants following 336 days in animal subjects and 41 days in humans yielded a predictive IVIVC of 0.9 to 1.2, and no indication of polyurethane or anastrozole degradation. A Tecoflex® EG-93A polyurethane implant formulated to deliver anastrozole for a once a year adjuvant treatment for estrogen receptor positive breast cancer shows promise for further development and commercialization.

REFERENCES
2. Hergenrother, R; Wabers, H; Cooper, S. Biomaterials. 1993, 14, 6, 449 – 458.