Anastrozole loaded-PLGA microspheres as a novel therapy to overcome noncompliance issues on breast cancer patients

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ABSTRACT SUMMARY

Controlled release formulations of Anastrozole-loaded PLGA microspheres were fabricated by using a novel Consject™ technology. In vitro and in vivo release studies demonstrate the feasibility of delivering anastrozole in a sustained manner from 3 weeks to 3 months.

INTRODUCTION

For the postmenopausal women with ER-positive breast cancer, aromatase inhibitors (AI) are widely prescribed at least for 5 years to prevent recurrence of cancer. Surprisingly, recent studies showed that adherence to taking these oral pills drops to 42% within 3 years post initial treatment. To make it worse, this poor adherence has to do with poor therapeutic outcomes such as less overall survival rate. Therefore, the novel therapy that can increase patient adherence is in need. To address this non-adherence of take AIs, i.e., to maximize therapeutic efficacy, we designed injectable depot formulation containing Anastrozole using biodegradable and biocompatible PLGAs.

Anastrozole-loaded PLGA microspheres were successfully prepared using novel Consject™ technology. We investigated pharmacokinetic profiles of our novel Anastrozole-loaded PLGA microsphere system in rats and dogs. The duration of therapeutically effective plasma concentration and the initial burst of each formulation were monitored and the formulations were further optimized to get more precise control of plasma concentration of Anastrozole.

EXPERIMENTAL METHODS

Preparation of drug-loaded PLGA Microspheres

Briefly, PLGA and Anastrozole were dissolved in non-toxic organic solvent. The dispersed phase was emulsified in 0.5% polyvinyl alcohol solution using a homomixer to make an oil-in-water (o/w) emulsion. Then, solvolysis agent was added to the emulsion. The mixture was subject to continual stirring to complete the solvolysis reaction. After addition of water, stirring was continued temporally and then the resultant suspension was collected by filtration. The hardened microsphere were re-dispersed, washed, and separated by filtration. The microspheres were freeze-dried.

Characterization of Anastrozole-loaded PLGA Microspheres

Each formulation accurately weighed and dissolved in acetonitrile. The solution was diluted with water and filtered with 0.2μm syringe filter. The filtrate was analyzed by using UPLC with UV detector system. Morphology, particle size distribution, water content and residual solvents were measured by a Scanning Electron Microscopy(SEM), laser-diffractometry (Malvern) Karl-Fisher moisture meter and Gas Chromatography(GC). In vitro drug release from microspheres was evaluated by a modified dialysis method.

Pharmacokinetic studies in Sprague-Dawley rats

Female Sprague-Dawley rats (220.4 ± 10.7 g) were used in pharmacokinetic studies including dose linearity study. Formulations were suspended in diluent and injected into hind leg muscle of each animal using 20G needle to administer 5 or 15 mg/kg anastrozole. Blood was collected through retro-orbital plexus using heparinized capillary tubes at predetermined time. Plasma samples were harvested by centrifugation for at 12000 rpm for 5 min and plasma were stored at -70 °C. Plasma concentration of anastrozole were determined
using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) detection.

RESULTS AND DISCUSSION

Anastrozole was successfully loaded into PLGA microspheres without using toxic methylene chloride. SEM measurement showed that drug-loaded PLGA microparticles possess a spherical shape free of irregular shapes which might be ideal for controlling drug-release profile. Laser diffraction measurement showed that the size of drug-loaded microparticles is less than 100 um. GC measurement showed that residual solvents are below the specification of ICH guideline.

Table 1. Characterization of the formulations

<table>
<thead>
<tr>
<th></th>
<th>Polymer Inherent Viscosity (dL/g)</th>
<th>Diameter (μm)</th>
<th>Drug Loading (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation 1</td>
<td>0.45</td>
<td>91.3</td>
<td>7.11±0.27</td>
</tr>
<tr>
<td>Formulation 2</td>
<td>0.5</td>
<td>87.1</td>
<td>9.41±0.09</td>
</tr>
<tr>
<td>Formulation 3</td>
<td>0.4</td>
<td>72.5</td>
<td>5.89±0.35</td>
</tr>
<tr>
<td>Formulation 4</td>
<td>0.4</td>
<td>66.7</td>
<td>8.61±0.11</td>
</tr>
</tbody>
</table>

Fig 1. In vitro release of anastrozole from microspheres.

The sustained release profiles of Anastrozole with low initial burst (24h: 1.8% ~ 6.4%) can be obtained as shown in Fig 1. The drug release rate was well controlled, allowing sustained release of Anastrozole from 3 weeks to 3 months by changing formulation factors.

Fig 2. Mean (S.D.) plasma concentration of anastrozole versus time curves obtained after single intramuscular injection of formulations to female Sprague-Dawley rats (n = 3 per group)

Pharmacokinetic profiles of Anastrozole were obtained as shown Fig 2. The drug release rate was also well controlled, allowing sustained release of Anastrozole from 3 weeks to 3 months in vivo.

This novel therapy might be more advantageous compared with once-a-day dosing of Anastrozole Tab, providing more patient compliance by reduced dosing frequency.

CONCLUSION

Anastrozole-loaded PLGA microsphere systems demonstrated the feasibility of delivering AIs from 3 weeks to 3 months as evidenced in vitro drug release profile. Pharmacokinetic studies revealed the possibility of delivering a therapeutically effective amount of Anastrozole in a sustained manner in vivo.

REFERENCES

3. Im H.Y.; Kim, J.; Sah, H. Biomacromolecules 2010 11, 776-786