Twice and Once Monthly Risperidone Loaded Microparticle Formulations

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ABSTRACT SUMMARY
Two controlled release formulations of risperidone were prepared using poly(lactide-co-glycolide) and compared to the marketed Risperdal Consta™ formulation. The formulations were made by different methods and were characterized for in-vitro release, content, particle size and water content. Method 1 reproduced the Risperdal Consta product with matching in vitro release profiles. Method 2 eliminated in the lag period and produced more constant in-vitro release over the period studied.

INTRODUCTION
Risperidone is currently marketed as a controlled release microparticle formulation (Risperdal Consta™) administered every 2 weeks, in part, to ensure better patient compliance over immediate release formulations. It stands to reason that a longer duration requiring fewer administrations might improve patient compliance further. To this end, Evonik has formulated an alternate, longer lasting microparticle formulation and compared it to the marketed product. Evonik also reproduced the risperidone formulation described in US Patent 6,194,006 (identified in the Orange Book under Risperdal Consta™) and compared to the marketed Risperdal Consta™ product as an internal control.

EXPERIMENTAL METHODS
The microspheres in this evaluation were prepared by two different solvent extraction processes. For Method 1 (described in US Patent 6,194,006), a discontinuous phase (DP) was prepared by dissolving a poly(lactide-co-glycolide) polymer in ethyl acetate and mixing with a solution of risperidone dissolved in benzyl alcohol. An aqueous continuous phase (CP) was prepared comprising 1 wt% polyvinyl alcohol (PVA) and saturated with ethyl acetate. The two phases were mixed by pumping together through a static mixer. The microspheres were hardened, collected on a sieve and subsequently rinsed with ethanol. Intermediate drying was accomplished by applying vacuum. The microspheres were re-slurried in ethanol and recollected on a screen. The particles were then reduced to dryness by vacuum.

For Method 2, an aqueous CP was prepared comprising 1% (w/w) PVA and saturated with dichloromethane (DCM). A DP was prepared by dissolving PLG and risperidone in DCM. The CP and DP were mixed by pumping together through a flow-through homogenizer stirring at 2400 rpm. Upon exiting the homogenizer, the emulsion was mixed with high purity deionized water (EasyPure System, ~18 mOhm resistance). The entire stream was collected in a tank and stirred at ambient temperature for 70 min. The microspheres were collected on a screen, rinsed with water, and air-dried.

The microparticles were then characterized for drug content, particle size, in-vitro release, and residual moisture.

RESULTS AND DISCUSSION
Table 1 shows the analytical data obtained for three lots (704-005, 704-009, 704-014) of microspheres prepared by Method 1. Also, presented for comparison in Table 1 are the results of analysis of one lot (704-017) prepared by Method 2 and one lot (4152BAPI) of Risperdal Consta™ analyzed as a control. Figure 1 shows that the mean in-vitro release profile of the formulations made by Method 1 have a low burst (< 2% at 24 hours) and a similar lag for 15 days (21%) when compared to Risperdal Consta™ (14%). The lot made by Method 2 had a 24-hour burst < 2%, and release continued rapidly and steadily to 17% by Day 2 and 62% by Day 15.
Table 1. Analytical Results

<table>
<thead>
<tr>
<th>Lot #</th>
<th>Risperidone Content, wt%</th>
<th>Water, ppm</th>
<th>Particle Size, µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>704-005</td>
<td>40.2</td>
<td>19</td>
<td>77.5</td>
</tr>
<tr>
<td>704-009</td>
<td>39.32</td>
<td>147</td>
<td>98.8</td>
</tr>
<tr>
<td>704-014</td>
<td>39.4</td>
<td>6</td>
<td>99.6</td>
</tr>
<tr>
<td>704-017</td>
<td>44.93</td>
<td>11724</td>
<td>63.4</td>
</tr>
<tr>
<td>Risperdal Consta™</td>
<td>39.18*</td>
<td>784</td>
<td>92.1</td>
</tr>
</tbody>
</table>

*Based on patent information

Figure 1. In vitro release comparison of the microparticles prepared by Method 1, Method 2, and Risperdal Consta™.

CONCLUSION

These results show that risperidone can be formulated as microparticles to produce in-vitro release profiles similar to Risperdal Consta™. Further, the lag period can be eliminated, if desired, to produce more continuous release over longer durations. Future work will focus on optimizing product yields and scale and decreasing the initial release of the longer duration formulation.

REFERENCES