ABSTRACT SUMMARY

The animal health industry maintains a strong interest in controlled release parenteral formulations and has seen pioneering innovation in drug delivery technology for both production and companion animals. Easy, ready-to-use products are preferred in the marketplace. This presentation will focus on an overview of sustained release injectables formed in situ and their use as veterinary parenteral products. SUCROMATE™, BUPRENORPHINE SR™, and MELOXICAM SR™ and LONGRANGE® (eprinomectin), an extended release prescription injectable parasiticide for cattle, will be discussed.

INTRODUCTION

Several types of in situ systems have been reported for veterinary applications, including those based on biodegradable polymer gel formation, sucrose acetate isobutyrate depot formation and lipid-based liquid crystalline phase transitions. All of these systems undergo a physical change to form a depot. Products used in human health, such as ELIGARD® (an injectable in situ forming depot) are packaged in single use, two-syringe mixing systems which would not be practical for cost effective mass administration in production animals. One challenge to the animal health industry formulators has been to develop a ready-to-use and easily injected extended release product. Recent advances have led to several new products, including a stable, ready-to-inject product, LONGRANGE, which was recently introduced into the cattle market.

EXPERIMENTAL METHODS

Three 10% w/v ivermectin formulations were made with the compositions shown in Figure 1. A 10% w/v ivermectin formulation compositions using 75:25 L:G PLGA

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>PLGA content (%w/v)</th>
<th>Solvent ratio Triacetin/Glycerol Formal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>20/80</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>35/65</td>
</tr>
<tr>
<td>3</td>
<td>6.7</td>
<td>50/50</td>
</tr>
</tbody>
</table>

Figure 1: Ivermectin formulation compositions using 75:25 (L:G) PLGA

Cattle (weighing 125-250 kg at treatment, n=5) were dosed with a subcutaneous front of shoulder injection (1 mg ivermectin/ kg body weight) and plasma levels monitored. The plasma levels are shown in Figure 2.

An eprinomectin formulation [LONGRANGE; each ml contains 50 mg eprinomectin, 50 mg PLGA (75:25) in a cosolvent system of NMP and triacetin] was prepared. Cattle (8-9 months of age, weighing 147-247 kg at treatment, n=42) were treated with a SC front of shoulder injection (1 mg/ kg bodyweight) once on day 0 with the ready to use formulation and the plasma levels monitored. The plasma levels are shown in Figure 3.

RESULTS AND DISCUSSION

The plasma profiles in Figures 2 and 3 show prolonged release of ivermectin and eprinomectin for 100-150 days. Figure 2 shows the variation in the release profile that can be obtained by varying the polymer concentration and ratio of the lipophilic solvent (triacetin) to hydrophilic solvent (glycerol formal) in vivo. Figure 3 shows a plasma profile for LONGRANGE corresponding to the period of expected efficacy of eprinomectin. The product prescribing information describes the duration of persistent effectiveness as: Lungworms (Dictyocaulus viviparous) 150 days, and Gastrointestinal Roundworms: Cooperia oncophora, Cooperia punctata and Trichostrongylus axei - 100 days, and Haemonchus placei, Oesophagostomum radiatum, Ostertagia lyrata, Ostertagia ostertagi - 120 days.
CONCLUSION

Biodegradable and nonbiodegradableinjectable sustained release solid materials such as implants and microspheres have been marketed since the 1980s. One of the drawbacks to these systems is the cumbersome administration to a patient. Researchers since the 1990s have investigated many types of in situ gelling systems with a variety of chemical compositions and methods of gelling. All are using (relatively) low viscosity fluids prior to injection and relying on a rapid physical form change into a release controlled depot upon injection. The combination of nonaqueous solvents, and the polymer requirements needed to obtain control over the release rate will also impact the viscosity of the product, manufacturing process, and administration. Careful selection of solvents, using a combination of hydrophilic and lipophilic solvents, and balancing the concentration of the active ingredient and polymer, have resulted in stable ready to use products which are being used in the animal health market place. This innovative approach has resulted in a product viscosity allowing LONGRANGE to be supplied in ready to use bottles for cattle dosing using automatic syringe equipment for use with the 250 mL and 500 mL presentations, an important consideration for cattle producers.

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REFERENCES

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