

Characteristics of phospholipid based depot injectable technology for poorly water soluble drugs

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INTRODUCTION and OBJECTIVES

The purpose of the current study was to develop a subcutaneous injection which is well tolerated and does not give rise to crystallization of the drug substance after dilution. Administration of PHA-244 as either detergent or solvent formulations resulted in serious local tissue irritation compared to the placebo formulations.

SupraVail™ Phospholipid (PL) concentrates in a water miscible solvent were explored as subcutaneous injectable formulations for the water insoluble anti-infective PHA-244. Formulations containing up to 70 % w/v phospholipid could dissolve 15 % PHA-244. The formulations showed good syringeability and no precipitation of the drug after dilution with an excess of water. The local tolerability and pharmacokinetics of various formulations were explored after subcutaneous injection into cattle. A slow release pattern over a two week period and excellent local tolerability at the injection site were observed from viscous lipid reservoirs that formed *in vivo*.

RESULTS and DISCUSSION

1. Syringeability

Syringeability was tested using a 2 ml syringe with an attached 18 G needle. The needle was dipped into the inverted test sample and the time needed to fill the syringe with 2 ml of each test formulation was recorded. Results are presented in Table 1 as the time, in seconds, to withdraw 2 ml.

Formulation (all contained 10% w/w PHA-244)	09 (50% SPC, 20% P80, 20% ethanol)	10 (70% SPC, 20% ethanol)	11 (55% SPC, 27% MCT, 8% ethylactate)
Physical stability	> 4 months 4°C and RT	> 4 months 4°C and RT	> 1 month 4°C and RT
Syringeability 2ml	10 s	15 s	55 s

Table 1 Syringeability of formulations

2. PHA-244 Solubility

All formulations dissolved PHA-244 to form clear liquids. PL increased the solubility of PHA-244 in the formulation by x2 up to 15%w/v of PHA-244. Formulations were diluted x10 with water and the resulting dispersions were inspected microscopically for precipitates. A lipid to drug ratio of 5 to 1 was required to maintain the drug in solution upon dilution in aqueous media.

3. Local Tolerability

The local tolerability of three PL formulations containing polysorbate 80 (P80) (09), solely PL (10) and medium chain triglycerides (MCT) (11) and corresponding placebos (data not shown) were examined after subcutaneous injection (one cow per formulation) up to 11 days. Results are shown in Table 2. The placebo formulations were well tolerated. Only formulation 09 with PHA-244 showed unsatisfactory results compared to the placebo administered to the same cow. In agreement with previous experience, this effect was probably caused by precipitation of PHA-244 aggravated by the P80. Only the formulation (10) containing ethanol and phospholipid showed acceptable local tolerability and acceptable viscosity for injection through a 40 mm, 14-18 G needle.

Formulation	09	10	11
Day 1	7 x 7	9 x 8	7.5 x 7
Day 7	10 x 11	7 x 6	5 x 6
Day 11	8 x 7 x 3	Nodule 3 x 4	Very thin Layer

Table 2 Local tolerability in cattle after sub cut injection of formulations (at a volume of 18- 22 ml and a dose of 10 mg PHA-244/kg) N.B Surface area of swelling in l x b in cm; if significant swelling was observed, the height (cm) of the swelling is also stated

METHODS

PHA-244 is a poorly soluble (1 µg/ml water) anti-infective. PHA-244 was solubilized in various phospholipid (SPC) formulations (containing hydrophilic media and optionally other excipients) that could be sterile filtered. In the presence of an aqueous medium the PL formulations formed viscous lipid reservoir (liquid crystalline) at RT. The following parameters were examined:

1. Syringeability
2. Solubilization of PHA-244
3. Local tolerability
4. Pharmacokinetic profile

4. Pharmacokinetic Results

Following the tolerability results, formulations containing solely PL and PL with MCT were optimised and the three resulting formulations were tested in cattle. (see Figure 1 for results). The half life $t_{1/2}$ of the subcutaneous formulations was five to nine times longer compared to oral administration, suggesting a pronounced slow release from the injection site. As a consequence, the profile of the active metabolite of PHA-244 reached a maximum (C_{max}) of only 1000 - 2300 ng/ml compared to 9000 ng/ml after oral administration. This slow release effect with lower C_{max} and higher T_{max} was even more pronounced for formulation 0042 compared to the other two formulations.

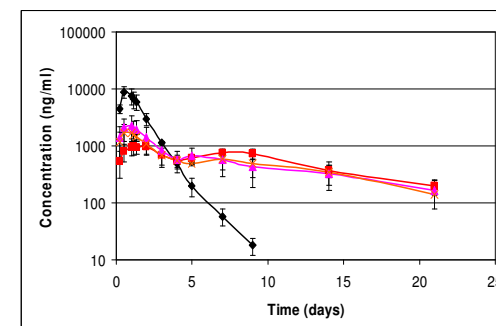


Fig. 1. Mean plasma profiles [ng/ml] ± S.D. (n = 3), of PHA-244A in cattle after subcutaneous administration of phospholipid based injectable PHA-244 formulations (0042, 00/43, 0044), compared to oral administration of a suspension of PHA-244 (•••)

CONCLUSIONS

SupraVail™ Phospholipid formulations can be used as an alternative to (depot) suspensions for subcutaneous injection of lipophilic compounds (such as CNS, steroids, anti-inflammatories). Expensive sterile crystals are not needed and sterilization by means of aseptic filtration is possible.

1. Sterile syringeable formulations with a high drug concentration and PL content can be prepared.
2. The high level of phospholipids prevented crystallisation of PHA-244 in the formulation and upon dilution/injection.
3. In *in vivo* tests, PL and PL/MCT formulations demonstrated excellent local tolerability at the injection site.
4. In *in vivo* tests, the formulations provided a slow release of the drug, probably by means of formation of viscous lipid reservoir in which the drug is solubilised.

 PHARES

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