



Research paper

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

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Abstract

Phospholipid concentrates in a water miscible solvent were explored as injectable formulations for the poorly water-soluble drugs, using the anti-infective PHA 244 as model substance. Formulations containing up to 70% w/v phospholipid could dissolve 15% PHA 244. The formulations showed excellent syringe-ability and no precipitation of the drug after dilution in an excess of water. The local tolerability and pharmacokinetics of the formulations were explored after subcutaneous injection into cattle. A slow release pattern over a 2-week period and excellent local tolerability at the injection site were observed. Considering the low manufacturing costs, related to the production of solutions, this SupraVail™ MLM (Membrane Lipid Matrix) technology is a cost-effective alternative to more expensive depot technologies for poorly water-soluble drugs with similar release characteristics, like sterile aqueous and oily drug substance suspensions, as cited in the literature.

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1. Introduction

Optimal subcutaneous/intramuscular administration of poorly water-soluble drugs poses an enormous challenge in pharmaceutical and veterinary sciences. Since water cannot be used as a solubilisation vehicle, three general approaches to achieve subcutaneous administration can be explored. The first approach is to make an injectable solution by increasing the solubility of the drug in water through addition of co-solvents, cyclodextrins, detergents and mixed micelles [1–3]. The second approach is to use aqueous-based dispersed systems, such as oil-in-water emulsions [4], drug substance- [1] suspensions, liposomal- [5] and microparticle suspensions [6]. A further approach is to use non-aqueous vehicles or injectable suspensions like oil solutions, oil–drug substance suspensions [1] and in-situ formed implants [7]. Aqueous dispersed formulations, non-aqueous solutions and dispersions are mostly used as slow release formulations.

Oil solutions and drug substance suspensions control the release for weeks [1] whilst polymer-based micro-particles and in-situ formed implants are claimed to last for months [7].

From a formulation perspective, solutions are easier to develop than the more complex suspension type of formulations. Unfortunately, to achieve adequate therapeutic drug levels of poorly soluble compounds, the solvent and/or detergent required may cause tissue irritation and tolerability problems at the injection site [8]. Furthermore, drugs with limited aqueous solubility may precipitate uncontrollably at the site of injection and possibly result in variable dissolution, release and bioavailability.

The objective of this study was to explore the characteristics of novel, solution type, phospholipid-based subcutaneous/intramuscular injection formulations for drugs with low water solubility with respect to local tolerability at the injection site and release characteristics. SupraVail™ MLM is a membrane lipid technology developed by Phares that maximises the bioavailability of poorly water-soluble drugs [9]. The technology is based on the preparation of drug–phospholipid complexes in which the drug is dissolved in the lipid (i.e. fatty acid) domain of the phospholipid membrane. These complexes

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