

Development of a preclinical intravenous formulation for a poorly water soluble antiviral using SupraVail™ Membrane Lipid Matrix Technology

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INTRODUCTION

Phares tested the feasibility of SupraVail™ Membrane Lipid Matrix (MLM) technology for an intravenous injectable for preclinical research of a novel lipophilic, poorly water soluble antiviral drug. The performance of the SupraVail™ formulations was compared with conventional formulations in an animal study.

PHYSICAL CHARACTERISTICS OF ANTIVIRAL

MW: Approximately 500

Ratio [drug] in liposomes/ [drug] in buffer pH 7.4: 6600 :1

Solubility in water: 0.8 µg/ml

Solubility in conventional aqueous 10 % hydroxypropyl-β-cyclodextrin: 35 µg/ml

The drug is very lipophilic and poorly water soluble.

DEVELOPMENT OF BIOLOGICAL TEST FORMULATION

In line with the high partition coefficient of the drug for liposomes, the drug appeared to have a high affinity for phospholipids, confirmed using Phares' ADAPT™ Compound Screen. As a result, complexation of the drug with only a seven-fold excess of phospholipid prevented precipitation of the drug after dilution with water.

Using 100 mg lipid/ml lipid dispersion, a drug concentration of 14.2 mg drug/ml could be achieved using SupraVail™ MLM technology. This corresponds to a 17,750 fold increase of drug solubility. In comparison, cyclodextrin technology resulted in a 50-fold increase in solubility.

Based on this finding, the SupraVail™ MLM technology was explored to develop an intravenous formulation. This concept relies on the use of a two vial system, one containing a stable diacyl lipid aqueous dispersion with small particle size and the other containing the drug substance dissolved in a suitable water miscible organic solvent. Shortly before use, the contents of the two vials are mixed and the lipophilic drug quickly associates with the MLM. After intravenous administration the drug spontaneously transfers from the MLM to lipoproteins/albumin and is further distributed in the body.

Results

The local tolerability at the injection site at a dose of 10 mg drug substance (DS)/kg body weight of the lipid dispersion containing 1 mg DS/ml versus

the placebo lipid dispersions (100 mg lipid/ml), was evaluated.

It was found that the injection vehicle with and without DS was very well tolerated.

The dose normalised mean plasma drug concentrations of the Membrane Lipid Matrix formulation after single i.v. injection of 1.5 to 3 mg DS/kg in male Wistar rats (n=3), in comparison with a conventional organic solution formulation of the DS (ethanol / PEG 400 / saline) are depicted in Figure 1. Interestingly, the collaboration partner also administered the same formulations orally; the resulting absorption/plasma profiles (dose normalised) are also depicted in Figure 1.

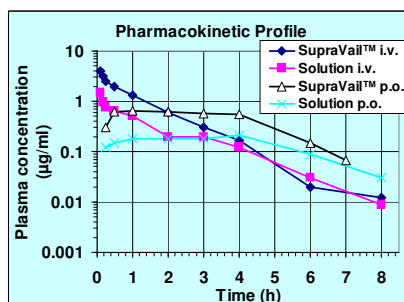


Figure 1, Normalised mean plasma drug concentrations of the Membrane Lipid Matrix formulation after single i.v. and p.o. application of 1.5 to 3 mg DS/kg in male Wistar rats (n=3), in comparison with a conventional solution formulation of the DS (ethanol / PEG 400 / saline)

In Table A, the corresponding calculated pharmacokinetic parameters are provided.

PK Parameter	SupraVail™	
	MLM formulation	Conventional solution
Intravenous administration		
AUC _{norm} [kg.h/L]	3.68	1.56
Oral administration		
AUC _{norm} [kg.h/L]	2.57	1.33
C _{max-norm} [kg/L]	0.603	0.281
T max [h]	1	4

Table A, Dose normalized mean pharmacokinetic parameters of test formulations.

The results in Figure 1 and Table A indicate that the SupraVail™ formulations show a superior bioavailability (BAV) after intravenous (2.4-fold better) as well as oral (1.9-fold better) administration in comparison with the organic solution formulation. The occurrence of precipitation of the DS after dilution in aqueous media (serum and GI tract fluids) may explain these striking differences in BAV. The oral BAV of the SupraVail™ formulation was 70 % compared to the absolute BAV (i.v.).

BENEFITS

- In less than six weeks an experimental intravenous formulation in a vehicle which was shown to have low toxicity and superior BAV compared to a conventional solution formulation was provided.
- The intravenous formulation enabled an uncomplicated assessment of the efficacy of the compound. Thus, oral formulations were evaluated more confidently, because the absolute BAV of the compound was then known.
- The MLM formulation was also useful as a highly attractive oral formulation with high BAV (70 %) which allowed additional testing of the compound without further formulation work.

CONCLUSIONS

- SupraVail™ Membrane Lipid Matrix is ideal for the formulation of a poorly soluble lipophilic drug for intravenous administration.
- The use of vehicles with low intrinsic toxicity in a two vial system allows fast track development of a safe and reliable intravenous formulation for lipophilic drugs.
- The flexibility of SupraVail™ MLM for intravenous administration represents a fast track development strategy equally suitable for toxicology, efficacy, pharmacokinetic and clinical studies by employing the same formulation principle throughout.

TECHNICAL SUMMARY OF RESULTS

Description	Result
Measured lipid affinity	High
Solubilisation enhancement in water compared to unformulated drug	X1000
Solubilisation enhancement using conventional cyclodextrin technology	x50
Bioavailability increase in man compared to partner's reference formulation	+100%