

Two-component, easy-to-use parenteral delivery system for poorly water-soluble drugs

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INTRODUCTION and OBJECTIVES

For poorly soluble compounds it is frequently difficult to develop intravenous dosage forms. The use of surfactants (e.g. polyoxyl-35-castor oil or polyoxyethylene sorbitan mono-oleate) are associated with hypersensitivity reactions in some patients, and the number of cases in which cyclodextrines were successfully used is limited. Co-solvent systems may lead to precipitation upon dilution after administration in the blood as the solubility typically drops dramatically. Phospholipids in the form of liposomes offer an opportunity to solubilise poorly water-soluble compounds. Solubilisation of the active with liposomes can effectively prevent precipitation of the drug at the injection site, and the small particle size of the liposomes represents no risk of formation of embolisms after intravenous administration. A recent commercial example of the use of liposomes for solubilisation is Visudyne®, (Verteporfin for injection; see Chowdhary et al. J. Pharm. Pharmaceut. Sci. 6(1):13-19, 2003). However, drug-loaded liposomal dosage forms are technologically demanding. For example, incorporating the drug into liposomes and maintaining physical and chemical stability of drug-loaded liposomes are often difficult tasks to achieve.

The objective of this study was to overcome these hurdles and to develop an *in situ* liposomal formulation concept (SupraVail™ MLM), which could then be used to assess efficacy, absolute bioavailability and toxicity of a variety of lipophilic compounds in both preclinical and clinical settings, without the risk of precipitation upon dilution and without the use of toxic excipients.

METHODS

Placebo liposomes were prepared by dispersing membrane lipids for 1 hour with a stirrer in an aqueous medium. The dispersion was homogenized at high pressure and then sterile filtered through a 0.22 micron pore size filter. Drug concentrate was made by dissolving drug substance and a stabiliser in a mixture of water miscible, physiologically compatible organic solvents.

RESULTS and DISCUSSION

A two-component system comprising a drug concentrate and a placebo liposome dispersion (ca. 50 nm diameter) could be developed. The drug substance concentrate is added to a clear isotonic lipid dispersion, so allowing control of the drug loading procedure. After mixing, an intravenous formulation is obtained in which the drug is dissolved in the lipid membrane. Drug concentrations up to 10 mg/ml were demonstrated, and - depending on the lipid affinity of the drug - concentrations up to 40 mg/ml are possible (Fig. 1 and Table 1). The dramatic improvement in drug solubilisation through the use of this *in situ* procedure can be more than 1000 times higher than that of the pure drug substance in water (often < 1 µg/ml).

The individual components (placebo lipid dispersion and drug concentrate) demonstrated adequate shelf-life, and the final injectable dispersion was physically and chemically stable for at least 4 hours. Upon dilution with 5% glucose, the liposomal dispersions were physically stable at room temperature for at least 24 hours. No drug precipitation was observed.

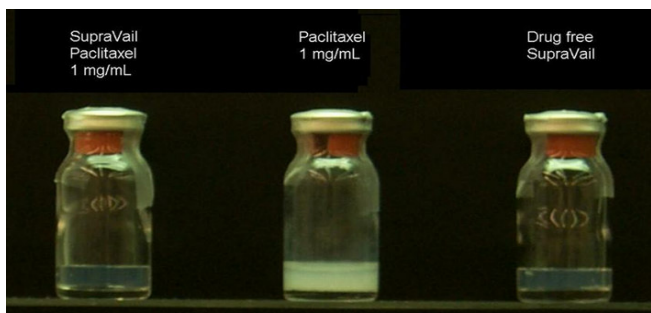


Fig. 1. Appearance of lipid dispersions before (right) and after loading with paclitaxel (left) in lipid dispersions, in comparison with the control (middle, drug concentrate added to plain water).

Drug Substance	R&D Phase	Solubility ¹ in Water (µg/ml)	Solubility ¹ in SupraVail™ MLM ² (µg/ml)	Increase in Solubility
Paclitaxel	0	0.4	1'000	2'500 ×
Cyclosporin	0	14	1'000	71 ×
Anti-infective I	0	0.8	1'000	1'250 ×
Anti-infective II	1	< 1	500	> 500 ×
Cardiovascular	0	10	10'000	1'000 ×
Anti-cancer I	0	< 100	10'000	>100 ×
Anti-cancer II	0	0.04	2'500	62'500 ×

¹1 At room temperature and pH 7 ²2 Based on 100 mg phospholipid/ml

Table 1. Increase in solubilisation of a variety of poorly water soluble compounds using SupraVail™ MLM technology.

After intravenous administration in animals the drug substance shows the same pharmacokinetics as compared to formulations comprised of pure solvent. This means that either the drug substance, which is molecularly dispersed in the membrane, is rapidly transferred from the lipid vesicles to other lipid domains in the blood circulation (e.g. lipoproteins) and/or the lipid vesicles disintegrate rapidly, so releasing the drug substance. For this reason, a change of body distribution compared to a pure solvent formulations is not to be expected.

Compared to pure solvent formulations, the SupraVail™ MLM concept contains a maximum of 10% v/v water miscible, pharmaceutically acceptable organic solvent. This method can add further value to i.v. products through Phares's patent protection of the loading process.

In sharp contrast to organic solvent formulations, SupraVail™ formulations show no precipitation of the drug substance upon dilution in the blood stream. For this reason, this new concept is a viable approach to determine reliably the efficacy, toxicity and absolute bioavailability of poorly water soluble drugs in pre-clinical and clinical research and has the potential to be used in a marketed delivery form.

CONCLUSIONS

This novel *in situ* concept provides a new method of preparing parenteral formulations of a wide range of lipophilic and even lipophobic, poorly water-soluble compounds for preclinical efficacy and toxicity testing and clinical testing, with the possibility to fast-track development from the early preclinical to clinical phase, without the need of extensive reformulation. Furthermore, this solubilisation can be achieved using naturally-occurring, biocompatible, FDA-acceptable lipids, without having to resort to high levels of irritating or toxic organic solvents or aggressive surfactant systems.

 PHARES

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