

Instant Solubilization of Poorly Water-soluble Drugs by *In-situ* Loading of Aqueous Phospholipid Dispersions Suitable for Parenteral Administration

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ABSTRACT: The features of a new, *in situ* method for solubilizing poorly soluble drugs (SupraVail™ Instant Solubilization) are demonstrated. The resulting formulations are suitable for parenteral administration in preclinical and clinical studies. The technique avoids drug precipitation upon dilution and circumvents the need for co-administration of high organic solvent concentrations. The method involves mixing a sterile solution of a poorly water-soluble drug in a water-miscible organic solvent (the “transfer medium”) with an excess of a sterile, stable, phospholipid dispersion prepared by high-shear homogenization. The influence of several mixing parameters which may affect the utility and viability of the method for two drugs, namely diazepam or cyclosporine A, are examined in detail. The resulting transparent dispersions were analyzed for presence of insoluble particles, transmission, particle size, and degree of solubilization. It is found that solubilizing efficiency is mainly determined by the drug and the phospholipid-to-drug ratio in the final dispersion. Complete and instant solubilization is obtained by using negatively charged phospholipids in the transfer medium. Variations in the mixing conditions, such as fast addition compared to slow addition, no shaking (agitation) versus shaking during mixing, stirring after mixing, and temperature variations of the lipid dispersion do not significantly affect the reproducibility of the method.

KEYWORDS: In-situ solubilization, Phospholipids, Liposomes, Parenteral, Poorly water-soluble drugs, Cyclosporine A, Diazepam.

Introduction

Solubilizing excipients in oral and injectable formulations for poorly water-soluble (lipophilic) drugs were recently reviewed (1). Vehicles employing buffers/pH adjustment, water-miscible solvents, synthetic surfactants (e.g., Tween® and Cremophor®), oil-in-water (o/w) emulsions (2), and cyclodextrins are frequently used for solubilizing lipophilic drugs for parenteral application. Due to their low toxicity profile (3, 4), phospholipids are employed as solubilizing excipients for parenteral use. Firstly, in combination with glycocholate, they form mixed micelles which can solubilize the lipophilic compounds, for example, diazepam (5–7) and lipophilic vitamins Konakion® MM

paediatric (2.2%), Konakion® (1.9%), and Cernevit®, all multivitamins for infusion. Secondly, when phospholipids are used alone, they form liposomes (1). For the amphipathic, poorly water-soluble compound amphotericin B, liposomes are used to replace the cholate salt in the traditional formulation as solubilizer of the drug and to improve pharmacokinetics (8). Recent worldwide approval of Visudyne™ (Verteporfin® for injection) confirms the ability of liposomes to solubilize a highly lipophilic drug, such as benzoporphyrin, for parenteral delivery (9, 10). In both of these examples, the lipophilic drugs are associated with the fatty acid domain of the phospholipid bilayer membrane of the liposomes.

Small unilamellar liposomes (SUVs) are prepared with high-shear/high-pressure homogenizers. This method has been used in the pharmaceutical industry for many years for injectable o/w emulsions. Given suitable phospholipid compositions and a validated protocol,

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