MIXED MICELLES AN UNDERESTIMATED NANO-FORMULATION FOR PARENTERAL DELIVERY OF POORLY WATER SOLUBLE DRUGS

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Mixed micelles comprising phospholipids (soybean phosphatidylcholine) and bile salts, pose, besides oil-in-water emulsions, using phospholipids as emulsifier, and liposomes, alternative phospholipid-based formulation options to solubilize poorly water soluble drug substances for intravenous administration. In these formulations the phospholipid is added to the bile salt to eliminate its hemolytic properties[1]. Minimum weight ratios of bile salt to phospholipid of 0.7-0.8 are needed to obtain clear solutions[2]. Mixed micellar formulations can be prepared by e.g. dissolving the phospholipid component in an aqueous solution of the bile salt, followed by dissolving the drug substance. The aqueous mixed micellar formulation is sterilized by means of sterile filtration and when needed lyophilized. This type of formulation was the first mentioned in the literature in 1909 by B. Moore[3]. In 1916, H. Wieland mentioned the use of mixed micelles to solubilize poorly water soluble drugs[4]. In 1976 Hoffmann La Roche patented a mixed micellar formulation for diazepam[5]. Since then mixed micelles formulations are used in a few injectable and oral products (Konakion MM) to solubilize poorly water soluble drug substances or vitamins for intravenous administration (Cernevit). However, since decades this technology is not being used anymore in new products, which is remarkable, considering the many advantages of this technology: - the excipients are used in marketed products in the EU and USA, indicating adequate stability and acceptance by regulatory authorities,

- the excipients are biocompatible and are natural components present e.g. in blood,
- the excipients are available in parenteral quality,
- they can be produced using relatively simple technologies,
- they have no risk for anaphylactic reactions compared to synthetic solubilizers like e.g. Tween, Cremophor and Solutol; toxicity testing of mixed micelles has been published
- they are suitable for oral as well as parenteral formulation and accepted for pediatric use.

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Peter van Hoogevest, is a pharmacist by training (Utrecht University in The Netherlands), who got his PhD degree in biochemistry 1984 at the Utrecht University in The Netherlands. In 1994 he received the degree of Privat Dozent in pharmacy at the University of Basel, Switzerland.

His industrial career started at the Biovet Group of the Animal Health Division of Ciba-Geigy Ltd. (Basel) in 1984. Shortly thereafter he obtained a position at the Novel Dosage Form Department of Pharmaceutical Development of the Pharmaceuticals Division of Ciba-Geigy Ltd. After having several positions at this department at Ciba Ltd. and Novartis Ltd. he founded in 1998 together with colleagues of the Pharmaceutical Development Department and reputed industrial managers and scientists the company ADD Advanced Drug Delivery Technologies (Muttenz, CH) and became CEO of this company and was member of the Board of Directors. In 2000 he joined Phares Drug Delivery AG (Muttenz, CH), a company specialized in the delivery of poorly water soluble drug substances, as Managing Director and COO and member of the Board of Directors. Since 2012 he is Managing Director of the Phospholipid Research Center, Heidelberg and Head of the Scientific Department (including the Development Department) of Lipoid GmbH, Ludwigshafen am Rhein, Germany.

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