

Rheological Changes of Parenteral Emulsions During Phase-Inversion Emulsification

R. Márquez,¹ J. Bullón,^{1,2} L. Márquez,¹ A. Cárdenas,² M. I. Briceño,¹ and A. Forgiarini^{1,3}

¹Laboratory FIRP

²Laboratory of Mixing, Separation and Industrial Synthesis

³Laboratory of Polymers and Colloids, University of Los Andes, Mérida, Venezuela

An efficient emulsification procedure for parenteral soybean oil-in-water, based on current know-how on transitional inversion, was investigated. A fine droplet size lipid emulsion was produced using much lower mechanical energy than the typical industrial process. The aqueous phase was added gradually during mixing and various rates of water addition, as well as surfactant concentration, were evaluated. It was found that as addition rate and surfactant content increased, flow behavior changed significantly at intermediate water content, becoming highly viscoelastic. This behavior was related to the formation of a liquid crystalline phase that, at later mixing stages, turned into small droplets.

Keywords Formulation engineering, parenteral emulsion, phase inversion, rheological behavior

1 INTRODUCTION

A parenteral medication may be formulated as an oil-in-water emulsion in which the oil phase is a mixture of triglycerides and the emulsion is stabilized by means of natural emulsifiers such as lecithin. These emulsions are administered intravenously and may be used as a source of calories and fatty acids that are essential for patients or neonates, whose medical condition makes them unable to obtain adequate nutrition in a normal way.^[1]

Lipid emulsions are also important in the administration of liposoluble drugs that the organism does not adsorb efficiently when drugs are dispersed in an aqueous phase. They may also perform as vehicles for controlled drug delivery.^[2,3]

Parenteral emulsions must fulfill pharmacopoeia requirements; namely, they should be sterile, isotonic, nonpyrogenic, nontoxic, biodegradable, and physically as well as chemically stable. Besides, droplet size must be lower than 5 μm to prevent pulmonary embolism. The emulsion external aqueous phase should contain non-electrolytic components such as

glycerol to obtain isotonicity (280–300 mOsm kg^{-1}) in the blood media.^[3,4]

The emulsifying agent used in parenteral formulations is usually lecithin, which is a mixture of phospholipids found in the biological membranes of living organisms and, in consequence, can be totally biodegraded and metabolized. Lecithin composition depends on its origin, either egg yolk or soybeans. The principal components of lecithin are phosphatidylcholine and phosphatidyletanolamine.^[5]

The current methods of parenteral emulsions manufacturing can be divided in three stages: pre-emulsification, homogenization and sterilization.^[2,3] In the pre-emulsification step the components solubilization is achieved by adding the hydro-soluble constituents into the aqueous phase and those that are liposoluble into the oily phase.^[6] Next, a coarse emulsion with droplet size between 1 to 5 μm is produced using a high shear mixer, usually adding the oil phase over the aqueous phase at 70°C.^[7]

The homogenization step consists in refining the resulting coarse emulsion by means of high-pressure homogenizers or microfluidizers^[8] which operate at pressures higher than 1000 bar. At the end, a fine and monodisperse emulsion is obtained (0.1–.5 μm). The pressure and number of cycles that the emulsion has to go through the equipment depend on the required droplet size.^[9,10]

The final stage, which is sterilization, may also involve mechanical filtration.^[10] The pH is adjusted to minimize lecithin hydrolysis; the emulsion is filtered through membranes and then sterilized using an autoclave.^[3]

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Address correspondence to A. Forgiarini, Laboratory FIRP, University of Los Andes, Mérida, 5101, Venezuela. E-mail: anafor@ula.ve