# CHAPTER I

# INTRODUCTION

Oil in water submicron emulsions for intravenous administration are hetero geneous systems in which an oil is dispersed as droplets in aqueous phase and stabilized by phospholipids. They have a long history of use as an intravenous source of nutrition because the emulsified oil droplets are similar in structure to chylomicron, which is fat globules ranging from 0.5 to 1 μm in size and found in the venous system after the ingestion of dietary fats. Moreover, it would be expected to be metabolized via the same pathway as natural chylomicron. On the basis of these characters, they have been recently gaining attention as drug carriers for poorly water soluble drugs. The hydrophobic domain of oil droplets contribute the solubilization phase for lipophilic drugs resulting in possible application as drug carriers. In addition, the potential pharmaceutical applications include use as sustained release system and vehicle to deliver drugs to the target sites (Prankerd and Stella. 1990). Intralipid® was the first approved intravenous emulsion and has been used as a parenteral nutrition supplement for more than 30 years ago. It is a 10 or 20% lipid emulsion stabilized by 1.2 % fractionated egg phospholipids in 2.5% aqueous glycerol.

In 1985, Groves and co-workers (Groves, et al. 1985) suggested that the theoretical calculation amount to achieve a monomolecular film covering the oil droplets of 10% Intralipid® is only 50% of the phospholipids. It is noticeable that an excess of phospholipids is used in order to stabilize the parenteral emulsion by causing the formation of more complicated structures in the aqueous phase. Therefore, phospholipids stabilized oil-in-water submicron emulsion not only form a high negative surface charge but also from the existence of complicated structures such as bi- or oligolayer and unilamellar liposomes to ensure a stable emulsion (Ferezou, et al. 2001; Ferezou, et al. 1994; Westesen and Wehler 1992). Drug incorporated in those submicron emulsion systems could be distributed through every portions of submicron emulsion such as oil phase, oil-water interface, aqueous phase and also the complicated structures previously mention. Although, the study of drug distribution through various phases of submicron emulsion is limited, the effectiveness of antioxidants in different lipid system including emulsion are widely

investigated (Frankel, et al. 1994; Huang and Frankel. 1997; Huang, et al. 1996a). Several studies manifest that the environment of antioxidants localization has a major impact on their efficacy and stability. In bulk oils, the hydrophilic antioxidants, ascorbic acid and Trolox® were better antioxidants than their lipophilic analogues, ascorbyl palmitate and α-tocopherol. By contrary, in emulsion system the order of efficacy was reversed (Frankel, et al. 1994). Furthermore, Barclay and co-worker (1994) studied the partitioning of Trolox® in egg lecithin liposomes and found that the approximate 80% of Trolox® would exist in the aqueous phase of liposomes and this was suggested that Trolox® at least partially diffused into the lipid bilayer phase of egg lecithin liposomes. However, Trolox® exerted its antioxidant activity in liposome even when oxidation was initiated in the lipid phase. In 1996, Huang and co-worker evaluated the antioxidant effectiveness of α-tocopherol and its water soluble analogue, Trolox®, in different lipid systems. They found that the hydrophobic antioxidants were located in the oil phase and at the oil-water interface of emulsion system, whereas the hydrophilic antioxidants remained in aqueous phase and they apparently were less efficient (Huang, et al. 1996a; Huang, et al. 1996b). On the basis of these observations, the available reports therefore supported the concept that the localization of antioxidant is important for their activity in emulsion systems. However, the partitioning properties of particular antioxidants apparently depend not only on their chemical structure and relative polarity but also on the lipid substrates, surfactants, pH, temperature and composition of the phase (Barclay and Vinqvist. 1994; Pryor, et al. 1993). Unfortunately, there is no data available on how the physicochemical properties of drugs such as aqueous solubility, oil solubility and partition coefficient affect the partitioning behavior of those drugs in oil/water submicron emulsion for intravenous administration. However, methods of incorporation for drug containing in submicron emulsion could be considered. There are three incorporating methods commonly employed for incorporating drug in submicron emulsion. The first one is de novo emulsification, in which the incorporation of drugs in oil phase prior to emulsification process. Secondly, is the extemporaneous addition that is the addition of emulsion base to the concentrate solution of drugs dissolved in an appropriate solvent. The last one is directly shaking of the drug powder with the emulsion base. The last two methods are unsuitable for routine works because the precipitation of drugs could occur during storage period.

For the large scale manufacturing, de novo emulsification is desirable according to its particle size uniformity and stability during storage period.

Therefore, the objective of this research was to determine the influence of physicochemical properties such as aqueous solubility, oil solubility and oil-water partition coefficient, concentration as well as method of incorporation on the distribution of a model drug through various phases of phospholipids stabilized oil in water submicron emulsion for intravenous administration. For the physicochemical properties of drugs related to their chemical structures and molecular weights, the series of alkyl-4-hydroxybenzoate or paraben esters e.g. methyl-, ethyl-, propyl- and butylparaben were used as the model drugs. On the other hand, the benzodiazepines drugs e.g. alprazolam, clonazepam, diazepam and lorazepam were selected as model drugs due to their complex chemical structures which the physicochemical properties and molecular weights were unrelated.

Successful execution of this research will provide guidelines for the distribution study of other compounds which chemical structure as well as physicochemical properties resemble that of the model drugs. This will subsequently extrapolate where the investigated drug is located allowing the feasibility of drug containing submicron emulsion formulation for drug delivery system. In addition, the localization of hydrolytically susceptible drug is necessary to control drug stability since the hydrolysis instability of drug may be reduced if it is less deposit in aqueous phase than oil phase or oil-water interface. A better understanding of how the methods of incorporation affect the drug distribution will also be useful in developing or production of drug containing submicron lipid emulsion.