CHAPTER V

CONCLUSIONS

This present study is an attempt to delineate the effect of physicochemical properties of drug, concentration and method of incorporation on the distribution of model drugs into the different phases of submicron emulsion. Two series of model compounds were used for comparative characterization of drug distribution, a group of alkyl-4-hydroxybenzoate comprising methylparaben, ethylparaben, propylparaben and butylparaben and a group of benzodiazepine drugs comprising alprazolam, clonazepam, diazepam and lorazepam. Aqueous solubility, oil solubility and partition coefficient of alkyl-4-hydroxybenzoate compounds indicated these properties were correlated to their chemical structures. The oil solubility and partition coefficient of alkyl-4-hydroxybenzoate increased as the number of carbons in the ester increased and in contrast with their aqueous solubility whereas these physicochemical properties of benzodiazepine drugs were unlikely related to their chemical structure.

In this study, solid phase extraction cartridge was applied to extract all model drugs from other components in submicron emulsion. This technique was simple, rapid and required a small amount of solvent. The determination of the amount of model drugs by HPLC technique provided well resolved peaks of model drugs and the corresponding internal standard. Validation of this technique revealed a satisfactory recovery (80-100%), therefore, the proposed extraction method was suitable for the analysis of model drugs in submicron emulsion preparations.

Drug was incorporated in submicron emulsion using three incorporation methods, de novo emulsification, extemporaneous addition and shaking method. The preparations were characterized for mean particle size, zeta potential and pH. It was found that mean particle sizes of all drug containing emulsions were larger as comparing with submicron emulsion bases while zeta potential values were decreased. pH of the drug containing emulsions prepared by de novo emulsification and shaking method remained unchanged as comparing with submicron emulsion bases; except those prepared by extemporaneous addition, the pH were lower. Upon storage at ambient temperature for a period of seven days, the mean droplet size of emulsions became larger. In addition, the higher zeta potential as well as the lower in pH value was observed.

According to the difficulty in direct measurement of drugs in the different phases of submicron emulsion, it was necessary to separate the submicron emulsion in fractions and subsequently determined the amount of drug in each fraction. Therefore, ultracentrifugation technique was applied to separate submicron emulsion into different phases. After ultracentrifugation, submicron emulsion was separated into four phases, namely an oil phase, phospholipids rich phase, an aqueous phase and mesophase which contained liposome formed by the excess of phospholipids. The effects of physicochemical properties and concentration of drug on its distribution in various phases were examined. It was found that the highest oil solubility and partition coefficient compound was mostly localized in oil phase. The moderate lipophilicity compound was likely distributed to phospholipids rich phase and mesophase. The highest aqueous soluble drug was accumulated in the aqueous phase. However, the concentration of incorporated drug apparently had less effect on the distribution through various phases of submicron emulsion.

In addition, the effect of incorporation method on the drug distribution in various phases of submicron emulsion was examined. The phase of submicron emulsion that to be the first contact with the drug molecule during drug incorporation would play an important role in drug distribution in various phase of submicron emulsion. By extemporaneous addition, dimethyl isosorbide was used for drug solubilization prior to incorporation into emulsion base. Dimethyl isosorbide is miscible with water, so the dissolved drug first contacted with water, the external phase. As well, the primary phase of emulsion that making contact with drug compound in shaking method was also aqueous phase. Based on the data obtained from this study, it was found that drug mostly localized in oil phase for drug incorporating by de novo emulsification. However, the presence of drug in oil phase was observed in the drug incorporating method of extemporaneous addition and shaking method. This implied that dimethyl isosorbide which was used as solvent for dissolving drug in extemporaneous addition enhanced the partition of drug to inner oil phase. In addition, shaking force and period of shaking might assist drug partition into the inner oil phase in shaking method. The extemporaneous addition and shaking method allowed an investigated drug accumulating in an aqueous phase and mesophase which coexisted in aqueous phase before phase separation. Therefore, these observations suggested the possible influence of physicochemical properties, concentration and incorporation methods on the drug distribution through various phases of submicron emulsion.