CHAPTER I
INTRODUCTION

Historically, the basic philosophy behind the development of drug therapies was to enhance drug action as much as possible. For this reason, R&D pharmacists have been developing novel dosage forms and new techniques to take drug into the body. The greater attention has been focused on the development of sustained and/or controlled drug delivery systems. The advantages of these systems are to reduce the frequency of dosing and/or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery, and reducing adverse side effects (Grass IV and Robinson, 1990).

The route of administration is one factor that has a significant impact on the therapeutics outcomes of drug (Li and Robinson, 1987). Parenteral route is one approach to take the sustained and controlled drug delivery systems into the body. The drug can be directed to the intended site of action, and must be able to avoid interactions with other sites within the body. It can produce effects at a site of injection or being absorbed into the circulating systems and the target sites, respectively, depending on sites of injection and the properties of drug delivery carriers. The intravenous, subcutaneous, intramuscular, intraperitoneal, and intrathecal routes are all examples of parenteral routes of drug administration (Leung, Robinson, and Lee, 1987).

Colloidal carrier is one approach for the controlled delivery of drugs and active substances by the parenteral route, especially intravenous administration (Couvreur, Dubernet, and Puisieux, 1995). The desirable characteristics of an ideal colloidal drug carrier in parenteral administration are as follows: (i) the carrier can deliver a variety of agents; (ii) it can load drug in high capacity to carry a sufficient quantity of drug per unit carrier; (iii) it has an appropriate particle size for each anatomical compartment, such as it should be lower than 1 μm for intravenous administration but may be higher for intramuscular or subcutaneous administrations; (iv) it can prolong drug effect due to longer circulation time as compared to free drug

and minimize systemic drug release during intravascular transit; (v) it can protect the drug from metabolism and immune system recognition until it reaches the desire target site; (vi) it can interact selectively with the cells of the target site; (vii) it can retain the drug within the particle while in transit, and release the drug at the target site at the appropriate rate; (viii) it can increase the drug concentration at the required site of action due to a preferential sequestering of the particles by the desired target tissue, and release therapeutic concentrations to the target site without excessively loading the host within the carrier; (ix) it is biocompatible and reduces drug toxicity in the tissue; and (x) it is biological degradable compound (Leung et al., 1987; Petrak, 1993)

Colloidal drug carriers are currently under investigation including polymeric nanoparticles, liposomes, and lipid emulsions. There are, however, a number of drawbacks with respect to toxicity, product reproducibility, stability on storage, incorporation of drugs and their controlled release behaviors, which so far have prevented the widespread clinical application of these systems (Couvreur et al., 1995; Okamoto, Tsuda, and Yokoyama, 1981; Prankerd and Stella, 1990; Weiner, Martin and Riaz, 1989; Westesen and Siekmann, 1994).

The solid lipid nanoparticle (SLN) is an alternative particulated drug carriers system for parenteral administration. The idea behind the use of solid lipids is that the solid carrier matrix is expected to be stable against coalescence and should reduce the mobility of incorporated drugs thus preventing drug leakage from the carrier (Lucks, Müller, and König, 1992, Müller, Freitas et al., 1996). Their advantages are the low cytotoxicity due to their composition of physiological compounds, and the possibility of incorporating drugs for a prolonged drug release. Under optimized conditions they can be produced to incorporate both lipophilic and hydrophilic drugs and seem to fulfill the requirements for an optimum particulate carrier system. These solid lipid matrices offer the possibility to protect sensitive drugs from chemical decomposition (Müller, Mehnert et al., 1995).

Many researchers have studied the preparation of SLN in nanometer size range with narrow size distributions. Several techniques were developed to produce

the preparations. The lipid micropellet was prepared by spray dried and spray congealed methods, but this micropellet was too large for intravenous application (Eldem, Speiser, and Hincal, 1991). The lipid nanoparticle could produce by solvent-emulsification method developed by Sjöström and Bergenståhl (1992). This technique could produce the nanoparticles, however, some organic solvents might eliminate completely in the final step. Westesen, Siekmann, and Koch (1993) proposed two methods to produce SLN by sonication and high pressure homogenization. Furthermore, the SLN could be prepared by high pressure homogenization of a melted lipid dispersed in an aqueous surfactant solution. The optimum formulation having a particle size lower than 1 μm that was suitable for intravenous injection (Schwarz, Mehnert, Lucks et al., 1994; Müller, Mehnert et al., 1995).

SLN can be produced with a broad variety of lipid/surfactant combinations that form particles of different sizes, physical structures, electrochemical characteristics, and physiological properties. These compositions are exclusively based on physiological compounds to avoid the toxicological problems. Lipids such as tristearin, tripalmitin, trimyristin, or stearic acid have been used for the production of lipid nanoparticles in many studies (Cavalli, Caputo, Carlotti et al., 1997; Westesen and Bunjes, 1995; Westesen and Siekmann, 1997, 1998). Egg lecithin, anionic surfactant, is widely used in fat emulsion for parenteral products (Weiner, 1993). Poloxamer 407 is polymeric which could be used to stabilize dispersions. It is well toleration in cell cultures in the concentration up to 10% (Müller, Rühl, et al., 1997). Tween 80 is the non-ionic surfactant used in many parenteral products in the market in the concentration of 0.01 to 12% (Nema, Washkuhn, and Brendel, 1997).

From the previous works, the preparation and characterization of SLN were studied. Many lipophilic drugs were loaded into the lipid particles. However, there are no systematic studies on the properties of drugs that can be loaded into these carriers. Therefore, this study intended to investigate the effect of drug solubility on SLN characteristics, entrapment efficiency, and their *in vitro* drug releases. Triglycerides and fatty acid having melting point above the body temperature were chosen to be lipid carriers. Egg lecithin, poloxamer 407 and tween 80 were used to

stabilize lipid particles in aqueous medium in the concentration of 1-5% which could be used in parenteral products. Preparation parameters were evaluated before drug loaded SLN prepared. Four drugs with different solubility were used. Diltiazem hydrochloride was a representative of highly water soluble drugs. Theophylline was a sparingly water soluble drug. Piroxicam and ibuprofen were chosen to represent the water insoluble molecules. The results of this study may be useful for selection of drug to be loaded into these carriers and to develop these systems for delivering bioactive agents in pharmaceutical purposes.

Objectives of the study

The aims of this study were as follows:

1. To study the process of preparation, characteristics and drug release of SLN for using as long acting parenteral products.
2. To study the effects of pressure and number of cycle of homogenization on the particle size of fat emulsions.
3. To study the effects of types and amounts of stabilizer and solid lipid on the physicochemical properties and stability of SLN.
4. To study the effects of solubility of drug on the preparation, physicochemical properties, and *in vitro* drug release of SLN.
5. To study the reproducibility of the preparation and the possibility for developing to manufacturing scale.