CHAPTER I

INTRODUCTION

Parenteral administration of sparingly soluble substance is a major problem in the pharmaceutical industry. Several solubilizing techniques have been used in the past such as salt formation, cosolvent, complexation, liposomes. The use of cosolvents perhaps remains the method of choice for solubilzation of compounds. This could be attributed to the high efficiency of cosolvents to solubilize drugs as well as the ease with which this can be achieved. However, this technique has the potential to cause problems like chemical instability (El-Sayed and Repta, 1983), local pain and/or tissue damage upon parenteral administration (Brazeau and Fung, 1989; Gupta et al., 1994; Levy et al., 1989).

Microemulsions consist of water, oil, surfactant and cosurfactant, is a single optically isotropic and thermodynamically stable solution. Because microemulsions have unique physical properties, they have been attracted a great deal of interest in recent years as drug delivery vehicle (Attwood, 1994). Microemulsions have great potential as an vehicle for sparingly soluble substances because of their high solubilization capacity, high stability, protection of drugs from environment, potential for parenteral use and production on a large industrial scale without high-energy homogenization. Moreover, microemulsions can be used as sustained release formulation and improve efficacy of drugs, allowing the total dose to be reduced and thus minimizing side effects (Corswant et al., 1998; Gupta and Connon, 2000; Park and Kim, 1999).

- Many researchers incorporated hydrophobic drugs into the apolar oil phase of o/w microemulsion systems thereby enhancing their solubility (Garcia-Celma et al., 1994; Malcomson and Lawrence, 1993). Malcomson et al. (1998) studied the level of solubilization of testosterone propionate into 2% w/w oil in o/w microemulsions. They found that microemulsions exhibited a significant increase in solubilization over the corresponding micellar solution. Furthermore, the increase in drug solubility

observed in the microemulsion systems was not related to the solubility of the drug in bulk oil. For parenteral delivery, Park and Kim (1999) studied to improve the solubility of flurbiprofen in an o/w microemulsion suitable for parenteral administration. The mean droplet diameter of microemulsion containing less than 1% w/w of flurbiprofen was below 100 nm and the maximum solubility of flurbiprofen in the microemulsion system was found to be 10 mg/ml, eight times higher than in buffer.

Diazepam is one of the most widely used benzodiazepines in the treatment of anxiety states, acute alcohol withdrawal, skeletal muscle spasm, excitation states, premedication for surgical procedures, status epilepticus and other convulsive disorders (Ashton, 1994; Gustafson et al., 1981). Available dosage forms are tablet, syrup, emulsion, suppository and parenteral dosage form. The usual oral dosage for adults ranges between 2 to 10 mg, two to four times a day. For intramuscular or intravenous injection dosage for adults ranges between 2 to 15 mg that dosage repeated in three to four hours, if necessary. But no more than 30 mg should be given in an 8 hr period. Effective plasma levels vary from 0.2 to 0.5 μg/ml (Hanson, 1995). Some patients use diazepam for long term therapy. Therefore, the controlled release diazepam capsule (15mg/capsule) has been developed to achieve in one administration. Several studies have shown that the blood concentration of diazepam is maintained throughout the day after single dose of controlled release capsule so that the desired effect is stabilized without the patient having to take repeat dosing during the day (Montandon et al., 1986). Hence, the advantages of controlled release diazepam capsule over conventional dosage forms are increase of patient compliance, reduction of the fluctuation in plasma concentration and decrease dosing frequency.

In addition, diazepam is very slightly soluble in water (0.05 mg/ml) and degrades in aqueous solution by hydrolysis at the 4,5-azomethine bond (ring opening) resulting in the formation of an intermediate which undergoes further hydrolysis to produce 2-methylamino-5-chlorobenzophenone and glycine derivative (Lund, 1994; Macdonald et al., 1972). Therefore, drug delivery system as microemulsion is an alternative choice to increase both solubility and stability of diazepam. It could also control the release of drug. However, until now there has been no study that investigates controlled release of diazepam for parenteral administration.

Consequently, the objective of this study was to prepare diazepam o/w microemulsion as parenteral drug delivery system using commercially acceptable components (Nema et al., 1997; Powell et al., 1998). Soybean oil was chosen to be oil component. Tween 20 and tween 80 were chosen to be surfactant and glycerin, propylene glycol, polyethylene glycol 400 were used as cosurfactant. These materials are accepted to be used in parenteral products (Kibbe, 2000).

Objectives of the study

The aims of this study were as following:

1. To prepare and study the physicochemical characteristics of o/w microemulsions as parenteral drug delivery system.

2. To investigate the effect of type and amount surfactant, cosurfactant, and amount of oil on the microemulsions system with and without diazepam.

3. To study the drug release from o/w microemulsion and to determine the release kinetics of diazepam from o/w microemulsion.