CHAPTER I

INTRODUCTION

Indomethacin is a non-steroidal antiinflammatory drug which has widely been used in Thailand. Its pharmacological action is known to be an inhibitor of prostaglandins synthesis. Currently, indomethacin is used to treat degeneration and inflammation of joints or bones such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis. It is also indicated for primary dysmenorhea, ocular inflammation and patent ductus arteriosus (PDA)(1,2).

Indomethacin is a very low aqueous solubility drug. Its absorption is reported to be formulation dependence and the drug has been classified under drug demonstrating clinical inequivalence among its formulations (3). As seen,in previous report by Krasowska (4), he studied the absorption characteristics orally at a dose of 5 mg/Kg in rats. Result showed that solution of indomethacin in 60% polyethylene glycol 400 buffered at pH 2 gave the highest area under the curve value. This suggests that the extent of bioavailability of indomethacin may be controlled by its dissolution rate in the gastrointestinal fluid (5). In addition, previous studies (6,7,8) showed that indomethacin was unstable in alkaline aqueous solutions. Its kinetic of degradation is reported to be an apparent first-order process. The rate constant increased when temperature and ionic strength increased.

At present, numerous solid dosage forms of indomethacin are available such as capsules (25 mg), enteric coated tablet (25 mg), etc. The physicians and pharmacists found that it was very difficult to adjust or divide the dose of these solid dosage forms for children and patients who suffered from patent ductus arteriosus (PDA). This is because the dosage to be used is very low. Oral suspension of indomethacin is also available. However, it does not produce predictably blood level (9). It would be ideal to have indomethacin in the form of clear solution which is instantly compatible and stable in commonly used large volume parenteral products and other buffer solutions. This may be used as solutions, injections and ophthalmic solutions and can be substituted for the available solid dosage forms with lesser problems.

Recently, Martin and co-workers attempted to use the Extended Hildebrand Solubility Approach for the solubility of solids to predict solubility in pure and mixed solvents (10-16). The method provides a satisfactory empirical representation for the solubility of several drugs in binary solvents. However, no extensive experimental data regarding this approach for the solubility of indomethacin in mixed solvent system has been reported.

In this study, indomethacin was chosen to be a drug model based on its limited solubility in water and exhibiting bioavailability problem. Nonaqueous solvents such as alcohol, propylene glycol and polyethylene glycol were selected to form a binary solvent with water. The chosen solvents are non-toxic, nonirritating and nonsensitizing liquids which have commonly been used in parenteral

products (17).

In summary, the objectives of this study were to :

1. Predict the solubility of indomethacin in some mixed solvents by using method of the Extended Hildebrand Solubility Approach.

2. Determine and observe the compatibility and stability of selected indomethacin solution in commonly used large volume paranteral products and buffer systems of various pHs.

3. Study the possibility to prepare indomethacin in the form of solution, injection and ophthalmic solution by using appropriate mixed solvents.

The final results may offer greater latitude in the selection of appropriate solvents for the drug. This may be valuable in formulation new dosage forms of indomethacin in order to improve its bioavailability and therapeutic efficacy.