CHAPTER I

INTRODUCTION

Ketoprofen, is a highly potent and safe nonsteroidal antiinflammatory drug of the propionic acid derivatives. It's indication is analgesic in rheumatoid arthritis, osteoarthritis, primary dysmenorrhea and other pain. By orally, dose is 100-200 mg per day, 2-4 in divided dose because half-life in plasma is only 1-3 hours (Olin, 1995). In elderly, infant and the patient with recurrent peptic ulceration, active peptic ulceration, chronic dyspepsia that cannot take medicine orally, administration rectally is considered as an alternative route. Another advantage in rectal administration is that it is possible to avoid partly hepatic first pass effect. Besides the conventional dosage form, prolonged release suppositories can be prepared in order to achieve prolonged action medication for alleviation of pain during sleep being often helpful in reducing anxiety and the frequency of drug administration.

There are many reports presenting the procedures for preparation of prolonged release suppositories. Most of the techniques were dealt with alteration of each type of suppository base properties and/or modification of drug particle to obtain slow release in conventional suppository base. For hydrophobic suppository base, addition of hydrogenated soybean lecithin into Witepsol H-15 (Nakagima et al. 1988) slow-release indomethacin suppositories with sustained-plasma levels of rabbits were obtained (Nakajima et al. 1989). Results were also observed for diclofenac sodium suppositories which were sustained release by addition of lecithin to Witepsol H-15 (Nishihata et al. 1988). The other additive was sugar ester, which had similar properties to lecithin. It has been used in suppositories to enhance absorption of indomethacin in rabbits (Nakajima et al. 1990).

Gelling agent such as hydroxypropyl methylcellulose 4000 mixed with Witepsol W-25 were used to prepare controlled release of morphine (Moolenaar et al. 1995). Water absorbable polymer such as Poy® SA-20 (Nishiaki et al. 1990) was

employed to prepare sustained release diclofenac sodium suppository by absorption of the drug solution into Poy® SA-20, and suspended in the molten triglyceride suppository base.

For hydrophilic suppository bases, microencapsulation could be used to prepare controlled release of the drug (Nakajima et al. 1987). Microencapsulated indomethacin dispersed in polyethylene glycol showed sustained release characteristics.

The solid matrix technique is commonly used to prepare prolonged release suppositories. Technically, the base consisted of combination of poorly water soluble carrier and water soluble carrier. The slow erosion of poorly water soluble carrier provides prolonged action. There are several reports such as preparation of nifedipine sustained release suppositories using cellulose acetate phthalate (CAP)-polyethylene glycol 4000 solid matrix (Umeda et al. 1985). It showed sustained release effect in rabbits. Indomethacin was also used to prepare sustained release suppositories using hydroxypropyl methylcellulose acetate succinate-polyethylene glycol 2000 solid matrix (Ohnishi et al. 1987). Good sustained release characteristics were found in rabbits.

Eudragit L-100-polyethylene glycol 2000 solid matrix was used to prepare indomethacin sustained release suppositories (Ohinishi et al. 1988). Rectal administration in rabbits resulted in good characteristics for sustained release. Another was polycarbophil, which swell but insoluble in water. Sustained release indomethacin suppositories containing polycarbophil in polyethylene glycol 4000 (Hosny et al. 1995a) could be prepared. Polycarbophil as a bioadhesive increased absorption and improved bioavailability of indomethacin in dogs. Dihydroergotamine mesylate was also prepared as sustained release suppositories using polycarbophil (Hosny et al. 1995b). It revealed sustained release effect in dogs.

For ketoprofen, there are two reports for preparation of prolonged release suppositories. Chitosan was used to achieve sustained release properties (Tarimci et

al.1997). The results showed that sustained release effect were observed for *in vitro* studied, but the rectal bioavailability was reduced by nearly 40% in rabbits. Hydroxypropyl methylcellulose phthalate (HP55) in polyethylene glycol was also used as solid matrix bases (Ermis et al. 1995). *In vitro* release resulted in sustained release effect. This suggested that hydroxypropyl methylcellulose phthalate (HP55) might be useful as a vehicle for prolonged release preparations of ketoprofen in suppository form.

In this study, attempt was made to formulate prolonged release ketoprofen rectal suppositories in order to alleviate pain with duration 6-8 hours by using the minimum amount of prolonged release carrier. The solid matrix technique was used. The suppository bases were prepared in matrix form by using different PEG mixtures as water soluble carrier with Eudragit S-100 and hydroxypropyl methylcellulose phthalate as prolonged release (poorly water soluble) carrier. The suppositories obtained were evaluated for their *in vitro* and *in vivo* properties.

Objectives of this study

1. To formulate 100 mg prolonged release ketoprofen rectal suppositories by solid matrix technique using Eudragit S-100 and hydroxypropyl methylcellulose phthalate (HP55) as prolonged release carrier.

2. To evaluate *in vitro* properties and release characteristics of ketoprofen from 100 mg prolonged release ketoprofen rectal suppositories.

3. To compare the pharmacokinetics of prepared prolonged release rectal suppositories of ketoprofen in rabbits.

4. To compare the efficacy of Eudragit S-100 and hydroxypropyl methylcellulose phthalate (HP55) as prolonged release carriers on ketoprofen rectal suppositories with the reference hydrophobic base, Suppocire ®AM.