CHAPTER I

INTRODUCTION

Saquinavir mesylate (SQV), a poorly soluble drug, is a synthetic peptide analog and inhibitor of HIV-1 and HIV–2 protease (Gennaro, 2000). According to the low solubility of SQV administered orally, SQV has low oral bioavailability (4%) (McEvoy, 2004). In addition, metabolism of SQV is mediated by the cytochrome P-450 (CYP) and the isoenzyme 3A4 is involved more than 90% of metabolism.

At present, there is two commercially available products of saquinavir, i.e. Invirase® (Roache) containing an amount of SQV which is equivalent to 200 mg of saquinavir filled in hard gelatin capsule and Foryovase® (Roache) soft gelatin capsule containing 200 mg of saquinavir (http://www.rocheusa.com/products/fortovase/pi.pdf). For the later product, the solubility of saquinavir was increased by self-emulsifying technique to improve bioavailability. The bioavailability of the soft gelatin capsule formulation was estimated to be 331% of that of the hard gelatin capsule.

Niosomes, a lipid-based vesicle system, performs as colloidal drug carriers with the appropriate properties such as sustained release, drug targeting, improved therapeutic effect and reduced toxicity. It has been reported that niosomes could entrap both hydrophilic and lipophilic drug in bilayer structures. The system could enhance the solubility (Chen et al., 2003; Pillai and Salim, 1999), drug absorption (Fang et al. 2001; Arunothayanun et al., 1999a, and hence bioavailability of poorly soluble drugs (Varshosaz et al., 2003; Vyas and Venkatesan, 1999). Besides, lipophilic drug entrapped niosomes with size less than 10 μm could be absorbed via Peyer' patches in gastrointestinal tract (Eldridge et al., 1990).

In general, niosomes could be prepared by several methods, i.e. hand-shaking method (Baillie et al, 1985), sonication method (Rental et al., 1999), ether injection method (Baillie et al., 1986), dehydration-rehydration method (Arunothayanun et al, 1999a) and reversed phase evaporation method

(Arunothayanun et al, 1999a). These methods normally required energy input or relatively high rehydrating temperature, 60°C-80°C (Manosroi et al., 2003; van den Bergh et al., 1999). The rehydrating temperature maybe involved with phase transition temperature of nonionic surfactant. For example, niosomes of Span®60 with a phase transition temperature of 45°C could be rehydrated at 60°C (Manosroi et al., 2003). The nonionic surfactant with a low phase transition temperature may allow the vesicles to form with relatively small energy input or low rehydrating temperature.

There are several types of surfactants, i.e. nonionic esters, nonionic ethers and nonionic amide (Rieger, 1988). Nonionic ester and nonionic ether surfactants can form vesicles and relative stable under neutral conditions. However, unlike nonionic ester surfactants, nonionic ether surfactants can resist to chemical reaction, concentrated acidic/basidic condition. While nonionic amide surfactants are not commonly used in pharmaceuticals, they are widely used for cleansing products. Therefore, nonionic ester surfactants and nonionic ether surfactant are usually used to prepare niosomes.

Fatty alcohol ethoxylates (Polyoxyethylene alkyl ethers) are such a kind of surfactants which can resist to chemical reaction with concentrated acidic or basic condition (Rieger, 1988). It is expected that niosomes form with nonionic surfactant which can resist to physiological pH of gastrointestinal tract would provide the possibility of using this system for oral drug delivery.

The vesicular systems such as niosomes normally face with physical stability problems such as aggregation, fusion, leaking of vesicular system (Fang et al, 2001; Anssen et al., 1985; Wong et al., 1982). Dry products, e.g. proniosomes, which could be hydrated immediately and transform to be vesicles before administration would avoid these problems (Hu and Rhodes, 1999). It has been shown that proniosome-derived niosomes remained the efficiency in entrapment of both hydrophilic and lipophilic drug in bilayer structures. Proniosomes could be prepared by spray-drying method (Payne et al., 1986 and Hu and Rhodes, 1999) and slurry method (Blazek-Welsh and Rhodes, 2001) methods. Among these techniques, oven drying is simple technique and does not require special equipment.

In this study, the feasibility to develop proniosomes was investigated by using SQV as a model drug, and lactose. The poorly soluble drug could partition into bilayer membranes and hence its solubility could be enhanced. By choosing nonionic surfactants with appropriate properties, type, hydrophobic tail, hydrophilic head group, phase transition temperature, niosomes could be obtained at body temperature and resist to 0.1N hydrochloric acid and phosphate buffer pH 6.8. The size of niosomes desired would be smaller than 10 μm which can promote drug absorption by phagocytosis via Peyer's patch. The results obtained would indicate whether proniosome-derived niosomes could be a candidate for oral drug delivery system.

The objectives of this study were as follows:

1. To develop proniosomal granules
2. To study the physiochemical properties of proniosomes
3. To study the physiochemical properties of proniosome-derived niosomes in aqueous media at 37°C