# CHAPTER I

# INTRODUCTION

Psoriasis is a prevalent chronic skin disease which affects 0.1-3.0 % of world's population. It is characterized by hyperkeratosis and thickening of the epidermis as well as by increased vascularity and infiltration of inflammatory cells in the dermis (Linden and Weinstein, 1999). Psoriasis can develop at any age, but the first peak is between 10 and 20 years old and the second peak is at 57-60 years (Bajue, 2003). Various cutaneous expression of psoriasis may occur. The most frequent manifestation in more than 90 % of the patients is chronic plaque psoriasis. Less frequently occurring cutaneous manifestations are guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis (De Jong, 1997). The cause of psoriasis is unknown. Genetic and environmental factors are important in the etiology of the disease. Physical trauma and infection can be triggers (Bajue, 2003). There is presently no cure for psoriasis. Thus, the goal of treatment is to decrease the severity and extent of cutaneous lesion so that they no longer interfere substantially with a patient's employment, social life, and well-being. The currently available treatment for psoriasis can be divided into three main categories: topical, photo, and systemic therapies (Linden and Weinstein, 1999). Conventional topical treatments, such as emollients, coal tar, and ditranol, have been messy, cosmetically unacceptable, and of low efficacy while systemic therapies such as methotrexate, cyclosporine, and retinoid have suffered from significant side effects (De Jong, 1997; Linden and Weinstein, 1999; Dipiro et al., 2002).

Propylthiouracil (PTU), an old antithyroid drug, has immune modulatory effect, antioxidant activity and antiproliferative activity (Elias et al., 1993a). PTU has been shown to be useful orally alone (Elias et al., 1993a; Elias and Barr, 1995; Chowdhury and Mark, 2001; Kose et al., 2001) and in combination with methimazole in psoriasis (Elias, Goodman, and Rohan, 1993c; Elias, Goodman, and Rohan, 1993b; Elias et al., 1995). Treatment of psoriasis with PTU orally results in a good efficacy, low toxicity and

side effect and low cost as compared with other oral drugs. However, some side effects have been found such as hypothyroidism, skin rash, and gastrointestinal disturbance. PTU is a lyophobic drug with low water solubility (1:900 at 20 °C) and practically insoluble in chloroform. It is difficult to formulate into a homogeneous dosage form. The topical preparation of 5% PTU in propylene glycol and hydrophilic petrolatum produces significant resolution in patients with psoriasis (Elias et al. 1994). However, this conventional dosage form has limited solubilizing capacity for the drug. To maintain the desired drug concentration, there is a need for incorporation of an extra amount of crystalline drug into the preparation. This can cause irritation to the normal skin (Asavisanu, 1997; Scalf and Fowler, 2000; Friedman et al., 2002). No study investigating the effect of vesicular dosage forms that may be more efficient in delivery the drug to its target sites in the viable epidermis/dermis is available.

Particulate drug carriers such as vesicles and polymeric microspheres can increase drug delivery into deep skin strata via the follicular pathway (Nacht 1995; Niemiec, Ramachandran, and Weiner, 1995). Vesicles have a major advantage as drug delivery systems due to the amphipathic nature of their structural components. Structural arrangement into bilayers allows incorporation of a wide variety of compounds, both hydrophilic and lipophilic, into the vesicles. Compounds that show superior skin penetration with liposomes include clindamycin hydrochloride (Skalko, Cajkovac, and Jalsenjak, 1992), pyridine carboxylic acid phenyl ester, DL-α-tocopherol, and 2-(t-butyl)-4-cyclohexyl phenylnicotinate N-oxide (Schreire and Bouwstra, 1994), cyclosporine and α-interferon (Niemiec et al., 1995), and enoxacin (Fang, Hong et al, 2001). Phospholipid-based liposomes are the most widely studied vesicular dosage form. However, only a few liposomal preparations are commercially available for clinical use due partly to the high cost and stability problems. Niosomes, vesicles with non-ionic surfactants as structural lipids, have become an interesting alternative to liposomes, especially for dermal preparations (Ohta, Ramachandran, and Weiner, 1996; Agarwal, Katare, and Vyas. 2001; Carafa, Santucci, and Lucania. 2002).

Niosomes are analogous to liposomes as they also assume a bilayer vesicular structure. They first appeared in the seventies as a new feature of cosmetic industry. When compared to phospholipid-based vesicles, they have advantages of lower cost, better stability, and, thus ease of preparation and storage. In addition, niosomes may be prepared without use of organic solvent, while most methods of liposome preparation involve organic solvent. Similar to liposomes, niosomes have gained vast interest from researchers as potential carriers for topical skin delivery. Hofland et al. (1994) studied permeation of estradiol from n-alkyl polyoxyethylene ether niosomes. They showed that direct contact between niosomes and skin was imperative to exert the highest effect on drug transport. Niemiec et al. (1995) reported that niosomes enhanced topical delivery of peptide drugs into pilosebaceous units in the hamster ear model. Once the drug gets into the pilosebaceous units, it can freely diffuse to the viable epidermis, depending on the partition coefficient of the drug. Other drugs studied with niosomes include flurbiprofen and piroxicam (Reddy and Udupa, 1993), erythromycin (Jayaraman, Ramachandran, and Weiner, 1996), glycolic and glycerol (Ohta et al., 1996), cimetidine (Lieb, Flynn, and Weiner, 1994), α-interferon, and cyclosporine-A (Waranuch, Ramachandran, and Weiner, 1998). There are some reports comparing drug permeation between liposomes and niosomes which indicate that drug penetration from niosomes is superior to that from liposomes. These drugs are cyclosporine-A (Waranuch, Ramachandran, and Weiner, 1997; Dowton et al., 1993), α-interferon, and cyclosporine-A (Waranuch et al. 1998), enoxacin (Fang, Hong et al., 2001), lidocaine and lidocaine hydrochloride (Carafa et al., 2002), and cimetidine (Lieb et al., 1994).

Feasibility of vesicle formation depends on many factors such as nonionic surfactant structure, membrane additives, physicochemical properties of drugs, surfactant and lipid levels and method of preparation (Uchegbu and Vyas, 1998). The vesicle systems consisting of different compositions result in different properties and characteristics. In developing a successful formulation, one needs to characterize the resultant delivery system with regard to its physicochemical properties. Some properties of the vesicles which are normally characterized are drug entrapment, vesicle size, phase transition, physical stability, and drug release (New, 1997).

There are a number of reports on the study of factors affecting drug permeation across the skin from the vesicles. From those reports, the important factors include the thermodynamic state of the bilayer, size, melting point of lipid composition, and the existence of vesicular structure. Several in vitro and in vivo permeation studies were carried out to evaluate whether thermodynamic state of lipid composition of vesicles affected skin penetration of both hydrophobic and hydrophilic compounds. Hydrophobic compounds studied include triamcinolone acetonide (Yu and Liao, 1996), estradiol (Hofland et al., 1994), fluorescein (Perez et al., 2000), progesterone (Knepp, Szoka, Jr., and Guy, 1990), and betahistine (Ogiso, Niinaka, and Iwaki, 1996). These studies revealed that liquid crystalline state vesicles are more effective than gel state vesicles in enhancing drug permeation. On the other hand, the effect of thermodynamic state does not clearly affect permeation of hydrophilic drugs such as 5-fluorouracil (El Maghraby, Williams, and Barry, 2001), sodium heparin (Betz, Nowbakht et al., 2001), methotrexate (Trotta et al., 2004), and sodium ascorbyl phosphate (Foco, Gasperlin, and Kristl, 2005). In addition, some researchers reported that the vesicles composed of low melting point lipid like glyceryl dilaurate improve skin penetration of both hydrophilic and hydrophobic drugs such as glycolic acid and glycerol (Ohta et al., 1996), alpha interferon (Niemeic et al., 1995), and cyclosporine-A (Dowton et al., 1993; Niemeic et al., 1995; Waranuch et al., 1997; Waranuch et al., 1998).

El Maghraby, Williams, and Barry (2000a), Fang, Hong et al. (2001), and Carafa et al., (2002) studied the effect of the existence of vesicular structure on drug permeation across the skin. El Maghraby et al. (2000a) investigated the importance of liposome structure in permeation of oestradiol across the human skin and found that permeation of oestradiol from the liposomes was higher than that from lipid solution in 90% w/w propylene glycol. Similar results were observed in the study of Fang, Hong et al. (2001) who compared enoxacin permeation from liposomes and niosomes with physical mixtures of the lipid components and reported that permeation from the vesicles was superior to that from the physical mixtures. In another study, Carafa et al. (2002) investigated permeation of lidocaine and lidocaine hydrochloride from niosomes and

liposomes with micellar solutions of the same lipid. They also found that drug permeation from micellar forms was inferior to the vesicles.

As reported by du Plessis et al. (1994) and Sentjurc, Vrhovnik, and Kristl (1999), the effect of vesicle size and lamellarity of liposomes on drug permeation was minimal suggesting that intact vesicle transport does not occur. On the other hand, Verma et al. (2003) reported that drug penetration was inversely related to the size of the liposomes.

There are some studies to elucidate the mechanism of action of vesicles to improve skin drug delivery. The dominating mechanism of action in skin delivery of the vesicles may be: 1) the "free drug" mechanism: the drug is released from the vesicles and then freely permeates through the skin, thus drug permeation is correlated to drug release (Ganesan et al., 1984; El Maghraby, Williams, and Barry, 1999); 2) penetration enhancement of the lipid components: this mechanism is studied by skin pretreatment with empty vesicles and then compared drug penetration between co-treatment and pretreatment (Hofland et al., 1994; Fang, Hong et al., 2001; Honeywell-Nguyen, Arenja, and Bouwstra, 2003); 3) improved drug uptake: the vesicle may improve drug uptake by adsorption, fusion, and mixing with skin lipid. This mechanism is tested by dipping stratum corneum into the different vesicles and determining drug uptake (El Maghraby et al., 1999); 4) penetration of intact vesicles: some intact vesicles can permeate across the skin. It can be proved by comparing skin permeation from small vesicles (200-300 nm) with that from larger vesicles (> 500 nm) (Cevc, Schatzlein, and Blume, 1995; El Maghraby et al., 1999); 5) increased drug thermodynamic activity: this mechanism is tested by comparing the different entrapment efficiencies of formulations with drug permeation, (El Maghraby et al., 1999); and 6) the mechanism involving transepidermal osmotic gradient: elastic vesicles increase drug permeation by penetrating through the skin using transepidermal hydration force. This mechanism is thus tested by comparing drug permeation from vesicles under occlusive and non-occlusive conditions (Honeywell-Nguyen and Bouwstra, 2003). In addition, Waranuch et al. (1998) reported that the permeation of cycloscoporin-A from glyceryl dilaurate:cholesterol:Brij[®] 76

niosomes occurs as a result of dehydration of the liposomes followed by melting of the lipid components on the skin and permeation from liposomes is the same as that from lipid melts.

From previous reports, the investigation of formulation factors affecting drug permeation was focused on hydrophobic and hydrophilic drugs. However, the investigation of formulation factors affecting lyophobic drug permeation is not studied. PTU is a lyophobic drug and has a relatively low partition coefficient of 1.0 (Moffat et al., 2004). Thus, the effects of formulation factors on PTU permeation may be different from hydrophobic and hydrophilic drugs. If one knows about these factors, one can formulate the proper formulations that increase maximum or optimum drug permeation.

Therefore, the present study was aimed at formulating PTU niosomes and investigating some formulation factors affecting PTU permeation. In the formulation of PTU niosomes, some formulation factors affecting the properties of the vesicles were studied. These factors included type of surfactant, stabilizer, and aqueous media. The properties studied were entrapment efficiency, size and size distribution, phase transition, release study, and physical stability. The formulation factors affecting drug permeation included thermodynamic state, surfactant type, size, melting of the lipid component, and the existence of vesicular structure. In addition, this study also investigated the dominating mechanism of action of niosomes including increased drug thermodynamic activity, the "free drug" mechanism, penetration enhancement of the vesicles, and the effects of transepidermal osmotic gradient. The information obtained will be helpful in development of topical PTU noisomes for the treatment of psoriasis. Information data on the formulation factors affecting PTU permeation and the dominating mechanisms may be used to formulate the proper PTU formulations that increase optimum drug permeation and may provide useful information for other drugs with similar properties to PTU to be developed into practical formulations for topical skin delivery.

## Objectives

The specific objectives of this study were as follows:

1. To formulate PTU niosomes
2. To characterize PTU niosomes
3. To study the effects of formulation factors on PTU permeation from niosomes
4. To determine the dominating mechanism of skin drug delivery of PTU from various niosomal formulations