CHAPTER I

INTRODUCTION

Topical delivery has become of interest and is used more frequently to deliver therapeutic agents to the skin. When the desired site of action of a drug is the skin, there are many useful features of topical delivery over other routes such as oral and parenteral routes. Topical skin delivery can decrease systemic toxicity of the drug as well as decrease the dose and frequency of therapy and, at the same time, increase amount of drug in the skin and hence the effectiveness of therapeutic agents. Ease of administration is also advantageous to the patients. When applied to the skin, hydrophilic drugs can penetrate the skin and exert their therapeutic effects systemically. Hydrophobic drugs, on the other hand, can be localized in the skin and have local effects. Absorption of drug through the skin can occur via transepidermal and transfollicular pathways. Transepidermal route has long been accepted as the major pathway of drug transport through and across the skin. On the contrary, transfollicular route did not gain recognition until recently since the total area of hair follicles contributes only 0.1% of total skin surface (Lauer et al., 1995). According to newer lines of evidence, transfollicular route may have more significance in percutaneous absorption than it is generally assumed. Follicles are now believed to play an important role in percutaneous absorption of many therapeutic agents including hydrocortisone, niflumic acid, caffeine, and p-aminobenzoic acid (Illel et al., 1991). Sebaceous glands have been shown to contribute significantly to promote skin penetration of hydrocortisone and testosterone (Rolland et al., 1993). Dermal deposition and penetration of retinoic acid was found to be greater in skin with higher follicular density (Hisoire and Bucks, 1997). The specific role of the hair follicles in percutaneous absorption remains difficult to elucidate due to the lack of an adequate animal model to distinguish the two pathways of transport. Nevertheless, more recent studies have complied increasing quantitative data that characterize follicular transport as a complex phenomenon, which depends upon compounds and/or vehicle compositions (Weiner and Lieb, 1998).

Some scientific experiments have shown that particulate drug carriers such as vesicles (liposomes and non-ionic liposomes or niosomes) and polymeric microspheres can increase drug delivery into deep skin strata (Nacht, 1995; Niemiec, Ramachandran, and Weiner, 1995). A major advantage of vesicular drug delivery systems may due to the amphipathic nature of liposomal vesicles. It allows incorporation of a wide variety of hydrophilic and hydrophobic compounds (Chen and Chien, 1999). Liposomes may also serve as localized drug depots in the skin and the appendages, resulting in sustained release of the compounds (Fang et al., 2001). This may result in improved therapeutic indices of dermally active drugs while reducing the toxicity profile of those drugs. In addition, the stability of the drug can be increased when entrapped in vesicular structures (Rolland et al., 1993).

Clindamycin hydrochloride (Skalko, Cafkovac, and Jalsenjak, 1992), pyridine carboxylic acid phenyl ester, DL-α-tocopherol and 2-(t-butyl)-4-cyclohexyl phenylnicotinate N-oxide (Schreier and Bouwstra, 1994), cyclosporin and α-interferon (Niemiec et al., 1994), and enoxacin (Fang, Hong et al., 2001) are drugs that have superior skin penetration with liposomes over more conventional dosage forms such as solution, cream, and gel. There is some evidence that liposomal carboxyfluorescein (Lieb et al., 1992), hydrocortisone, and monoclonal antibody (Weiner and Lieb, 1998) can enhance drug penetration into the skin. A study in drug targeting to the skin with liposomes by the Upjohn Company showed that drug concentrations could be selectively increased at the desired site of action with appropriate liposomal formula. Transferol Follicular Delivery System, which uses liposomes and derivatives of natural oils to deliver its ingredients to the hair follicle, has been developed (The Revivogen Shop-Hairloss Pharmacy, 2001).

Although most topical liposome studies have focused on drug deposition into the stratum corneum, a growing number of studies have shown evidence of follicular delivery via liposomes. Targeted delivery to the pilosebaceous unit via liposomes and related vesicular drug carriers has been reported. An optimal particle size of the carriers for targeted delivery into the hair follicles seems to be less than 10 micrometers in diameter (Lauer et al., 1995). This pathway of transport is of particular importance for drugs with high molecular weight and for hydrophilic compounds.

The hair follicle can be a potential target of therapeutic agents. Of the three primary layers of the hair follicle, the outer root sheath is of greatest significance regarding drug delivery since this layer is continuous with the epidermis and physically indistinguishable from it (Osborne and Hatzenbuhler, 1990). Several other sites within the hair follicle may also be accessible for topical delivery of compounds. The sebaceous glands may be the target site since the etiology of some skin disorders is thought to be associated with their activity. These include acne and androgenetic baldness. Androgen receptors, as well as regulatory receptors for retinoic acid, epidermal growth factor and transforming growth factor, have been identified within the hair follicle (Lauer et al., 1995). These receptors may also be feasible target sites for drug delivery. Some forms of skin cancer might be linked to the mid-follicle bulge area (Lasic, 1998). This area, which possesses one of the fastest rates of cell division in mammals, is also seen as a potential site for targeted drug delivery. In addition to localized targets within the hair follicles, the possibility of systemic drug delivery via the hair follicles also exists. The vast complex of capillaries surrounding hair follicles and sebaceous glands may facilitate systemic transport of some compounds that enter the hair follicles. It is thus clear that targeting of drugs to the hair follicles via particulate carriers, such as liposomes and niosomes, is a promising strategy for percutaneous drug delivery.

In developing a successful formulation, one needs to characterize the resultant delivery system with regard to its physicochemical properties. Drug entrapment is of particular importance since all the effects observed in biological systems will usually be dose-dependent. For any drug delivery systems, high entrapment is desirable both therapeutically and economically. A system with high drug entrapment exposes the body to lower amounts of therapeutically inactive carriers that can be hazardous to biological systems at high levels. For phospholipid-based liposomes, high entrapment will reduce the risk of phospholipid overload when given systemically. It also means cost saving on pharmaceutical-grade phospholipids, the prices of which are usually high. Drug entrapment is also a good indicator for physical stability of the formulation and has been used accordingly (Uchegbu and Vyas, 1998). Drug entrapment in liposomes and niosomes is dependent on many factors including lipid composition, type and size of the vesicles, physicochemical properties of the drug, and method of preparation (Lauer et

al., 1995). These factors are interrelated and can be explained only on a case-by-case basis. Most of the studies with drug entrapment were focused on phospholipid-based liposomes. Direct studies on niosomes have been limited in number.

Most methods of preparation for phospholipid-based liposomes involve organic solvents and complicated procedures (Uchegbu and Vyas, 1998). The manufacture of liposome preparations is costly since all components and chemicals used must be of high purity. Traces of organic solvent have to be eliminated, which may not be an easy task. Besides, instability of natural phospholipids has compelled the pharmaceutical industry to turn to the more costly synthetic phospholipids. This has made liposomal preparations expensive and not practical for most drugs despite various intrinsic advantages of the delivery system. A comparable system that utilizes moderate-priced chemicals and can be prepared with ease would be highly desirable.

In recent years, synthetic non-ionic surfactants have been used to prepare vesicles. These chemicals have lower costs and better physical and chemical stability and may be prepared without use of organic solvents (Rieger, 1995). These non-ionic liposomes or niosomes are analogous to phospholipid-based liposomes in structure and are able to encapsulate both hydrophobic and hydrophilic substances the same way liposomes are (Uchegbu and Vyas, 1998). This new category of liposomes may be a good alternative to phospholipid-based liposomes, especially for percutaneous drug delivery. The physicochemical properties of niosomes, however, have not been as well characterized as those of liposomes due to the more diverse components used.

Drug entrapment in niosomes has been reported mostly for hydrophobic drugs such as flurbiprofen, estradiol, erythromycin, and cyclosporin-A (Reddy and Udupa, 1993). However, these authors did not study factors that might influence drug entrapment. Many drugs that are aimed for topical delivery to the skin may not fall into this category. Some of these drugs have lyophobic property, and it is problematic in dosage form design. Incorporation of these drugs into liposomes or niosomes may also be challenging. Supawadee Archawakom (1999) reported that propylthiouracil, a drug with low solubility in both water and chloroform, could be incorporated into phospholipid-based liposomes to an extent that was much higher than its aqueous solubility. Ratana Ratanatraiphop (2000) further reported that method of preparation affected entrapment

of propylthiouracil in liposomes. Propylthiouracil liposomes might be useful in treatment of psoriasis since they showed sustained antiproliferative activity in fibroblast cell culture. However, the high cost of the phospholipid used has made it unpractical to develop such formulation for clinical use. Other alternatives for propylthiouracil, including niosomes, are currently under investigation in our laboratory.

Minoxidil (MN), a pyrimidine derivative, was the first drug to become available for treating scalp hair loss (Michelet et al., 1997). The target site of action of the drug appears to be the pilosebaceous unit. It has lyophobic property similar to propylthiouracil, with intermediate partition coefficient between octanol and water ($K_{o/w}$ = 1.24). Thus, it seems to be another good model for drugs with lyophobic property to study factors that may affect drug entrapment in liposomes or niosomes. With regard to the use and method of application of the drug, niosomes seem to be a better delivery system for the study. The particulate nature of niosomes should promote deposition of the drug in the hair follicles. At the same time, the cost, availability of chemicals, and ease of preparation should allow further development for clinical use.

This study was aimed at investigating formulation and processing factors that might affect entrapment of minoxidil in niosomes. These factors include type of surfactant, presence of cholesterol, surfactant to cholesterol ratio, total lipid concentration, stabilizer, co-solvent, pH, and the loading process. The information obtained will be helpful in developing minoxidil, as well as other drugs with similar solubility property, into practical formulations for topical skin delivery.

Objectives

The specific objectives of this study were as follows:

1. To find suitable surfactants and surfactant/CHO ratios for minoxidil niosomes
2. To study the effect of equilibrating time on MN niosome entrapment
3. To study the effect of formulation factors on MN niosome entrapment
4. To study the effect of the preparation methods on MN niosome entrapment