CHAPTER I

INTRODUCTION

Topical skin delivery has become of interest and has been more frequently used to deliver therapeutic agents to the skin. Absorption of drug through the skin can occur via either transepidermal or transfollicular pathway (Singh et al., 2000; Mezei. 1993). 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 topical skin delivery than it is generally assumed. The pilosebaceous unit; which is composed of hair follicle, hair shaft, and sebaceous gland; is the major skin structure responsible for the transfollicular route. Several studies have shown that particulate drug carriers such as liposomes, niosomes, and nanoparticles can deliver active substances through the skin. In addition, these structures can specifically target the pilosebaceous unit as the site of drug action (Touitou et al., 1994; Trotta et al., 2004; Foldvari et al., 1993; Oommen et al., 1999; Schmid and Korting, 1994; Lboutounne et al., 2004; Shim et al., 2004; Schreier and Bouwstra, 1994; Fang et al., 2001).

Niosomes, a non-ionic surfactant-based vesicular system, can increase drug delivery into deep skin strata (Nacht, 1995). Niosomes may also act as localized drug depots in the skin and skin appendages, resulting in sustained release of dermally active compounds, thereby improving the therapeutic index of the drugs at the target sites as well as their toxicity profiles (Gregoriadis, Florence and Patel, 1993). Niosomes spontaneously form from self-assembly of non-ionic amphiphiles in the aqueous medium resulting in closed bilayer structures. Their structure is analogous to phospholipid vesicles (liposomes). In certain cases, cholesterol is required in the formulation of niosomes and vesicle aggregation may be prevented by inclusion of molecules that stabilize the system by repulsive steric or electrostatic effects. The low cost, greater

stability, and resultant ease of storage of niosomes have lead to the exploitation of these compounds as alternatives to phospholipid liposomes (Uchegbu and Vyas, 1998). A niosomal formulation for topical use, similar to a liposomal formulation, will be considered reasonable only if it provides several advantages over conventional formulations. The major advantage of niosomes lies in the vesicular structure of the system, as well as its amphipathic nature, which allows incorporation of a wide variety of hydrophilic and hydrophobic compounds.

Minoxidil, a pyrimidine derivative, was the first drug available for treating scalp hair loss (Meidan and Touitou, 2001). Aqueous solubility of minoxidil is limited. The approximate solubility of minoxidil in water at ambient temperature is only 2.2 mg/ml (Dennis, 1988). Minoxidil is available on the market in the form of scalp lotion, which contains high percentages of propylene glycol and ethanol (Median and Touitou, 2001). However, the target site of topical minoxidil is the pilosebaceous unit. Generally, only a small portion (less than 0.1-1%) of the drug from the scalp lotion is delivered to its pilosebaceous target site (Janoff, 1998), making the rest of the drug in the preparation a waste. Minoxidil is also photolabile with some yellow discoloration (Chinnian and Asker, 1995). The structure of N-oxide minoxidil has an unshared valence electron. It induces minoxidil to be liable with oxidation reaction. In addition, Pimolpan Pithayanukul (1988) reported that minoxidil solutions containing propylene glycol turn into pink color after being kept for some time, as a result of oxidation reaction between propylene glycol and minoxidil. Therefore, in terms of product development, minoxidil has a problem in drug delivery, as well as solubility and stability problems.

Formulation approaches may be used to solve these problems. A vesicular drug delivery system such as niosomes may direct the drug to its site of action more efficiently than the conventional dosage form. Additionally, niosomes have been proposed as systems capable of improving the stability of photosensitive drugs. For example, tretinoin has higher stability in vesicular suspensions than in methanol after UV irradiation (Manconi et al., 2003). Development of minoxidil into a niosomal preparation should also improve stability of the drug. However, the stability of photosensitive drugs in vesicular suspensions is also dependent on the vesicular structure and composition (Manconi et al., 2003). Scientific evidence is necessary to decide whether niosomes can

protect minoxidil from photodegradation. Drug release study is usually a mandatory step of topical drug product development. In vitro drug release can give information on the release profiles of drug in the vesicular formulation. Release studies have been used to evaluate drug delivery from the topical formulation and to check for the stability of both the drug and the vesicles. In vitro release profiles may also be used to explain the mechanism of drug stabilization by niosomes.

When niosomal preparations are applied to the skin for topical purposes, human skin as well as the underlying living epidermis and dermis has a tendency to be exposed to a relatively high concentration of surfactant. Thus, the irritation potential of topical preparations containing surfactants deserves a major interest from a dermatological viewpoint. Irritation potential testing is often performed in vitro, if possible, before the in vivo testing in animals and human exposure are introduced. The in vitro red blood cell assay is an alternative test that can assess irritancy in safety evaluation of surfactants (http://evam-sis.jrc.it). The test system is simple, inexpensive, does not require special equipment, is fast to perform, and is devoid of animal usage. It is proposed and validated as an alternative to the conventional Draize test (Pape, 2003). Thus, the test can be applied to evaluate the relative safety of topical niosomal preparation.

Feasibility of minoxidil niosome formation and drug entrapment as a function of various processing factors (type of surfactant, presence of cholesterol, surfactant to cholesterol ratio, total of lipid concentration, stabilizer, co-solvent, and pH of the aqueous phase) have been studied (Plookchit Chetratanont, 2002). The researcher found that it was possible to prepare minoxidil niosomes from commonly available non-ionic surfactants such as Span® and Brij®. However, there is still no information regarding physical and chemical stability of the resultant niosomal formulations. The information on drug release as well as the irritation potential of the preparations is also lacking. In order to develop minoxidil nisomes for clinical use, such information will be very helpful.

Thus, the purposes of this study were as follows:

1. To investigate physical and chemical stability of minoxidil niosomes

2. To study in vitro drug release from minoxidil niosomes, both to check for stability and as a prerequisite to further development of minoxidil niosomes for topical application

3. To evaluate the potential of niosomal formulation in improving the stability of photosensitive drugs such as minoxidil

4. To estimate the irritation potential of minoxidil niosomes.