CHAPTER I

INTRODUCTION

Minoxidil is a potent peripheral vasodilator used in treatment of resistant hypertension. A major side effect when administered orally for periods in excess of 1 month is hypertrichosis (Burton and Marshall, 1979). Consequently, topical minoxidil has been developed to try to improve hair growth in patients with alopecia areata and alopecia androgenetica.

The color of topical solutions prepared from minoxidil tablets (Loniten®) using propylene glycol, methylated spirit 95% and IMS as cosolvents changed from colorless to yellow after 3 months at room temperature, but there was no chemical degradation (Hainess-Nutt, Adams, and Bendell, 1984). In addition, Pimolpan Pithayanukul (1988) reported that minoxidil solutions containing propylene glycol turn into "pink" color after beeing kept for a period of time, as a result of oxidation reaction between propylene glycol and minoxidil. This study has indicated that heavy metal impurities in propylene glycol and minoxidil itself are the major catalysts in the oxidation reaction; and chelating agent such as EDTA sodium and/or antioxidizing agent, sodium bisulfite can stop this color change of the solutions.

Many clinical studies have found that topical minoxidil therapy is useful, efficient and has no serious side effect in inducing hair regrowth in male pattern baldness and some female alopecia. However, percutaneous absorption study of minoxidil in man has discovered that minoxidil is poorly absorbed through the skin (Franz, 1985). Some studies have showed that an evaporation of volatile components leads to a supersaturation and there may be a precipitation of minoxidil on the

application site (Chiang et al., 1989b; Tsai, Cappel et al., 1992; Tsai, Flynn et al., 1993).

Since minoxidil is insoluble in water, slightly soluble in propylene glycol and ethanol, therefore ethanol is used most as the solvent in topical solutions. To cope with these problems more effectively, we need to increase the solubility of minoxidil in topical preparations in hopes of minimizing the supersaturation problem of the solutions.

Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic cavity in the center. In aqueous solutions cyclodextrins are able to form non-covalent inclusion complexes with various types of lipophilic drugs. Encapsulation of a drug molecule will affect many of its physicochemical properties and can result in increased aqueous solubility and stability. These effects have been utilized in pharmaceutical formulations to improve bioavailability of drugs. Hydroxypropyl-β-cyclodextrin (HP-β-CD), one derivative of cyclodextrins, has been suggested to increase the flow of hydrocortisone through semi-permeable membranes (Loftsson, Frioriksdottir, Ingvarsdottir et al., 1994). Similarly, the release of betamethasone from gel and hydrophilic ointments was improved by cyclodextrins complexation (Otagiri et al., 1984).

Many investigators revealed that cyclodextrins could improve solubility of many water-insoluble drugs (Aboutaleb, Abdel-Rahman, and Ismail,1986; Duchene and Wouessidjewe, 1990a, b, c; Szejtli, 1990), stability (Glomot et al.,1988; Vincieri et al., 1988; Duchene and Wouessidjewe, 1990a, b, c), in vitro permeation of drugs from ointment preparations (Uekama, Otagiri, et al., 1985; Celebi, Kislal, and Tarimci, 1993) and ocular absorption of dexamethasone (Usayapant, Karara, and Narurkar, 1991).

Thus, this study was designed to investigate the effects of cyclodextrins on minoxidil solutions by using two kinds of cyclodextrins, β-CD and HP-β-CD. β-CD has internal diameter that is suitable for including the majority of active ingredients than α-CD and less expensive for its use in pharmaceutical manufacturing (Duchene and Wouessidjewe, 1990a, b). HP-β-CD, because of its higher aqueous solubility than natural cyclodextrins has less tendency of the complex to crystallize than β-CD complex (Bekers et al.,1991). To investigate the solubility enhancing property of cyclodextrins, solubility studies were done according to Higuchi and Connors (1965). For the purpose that cyclodextrins will improve stability and percutaneous absorption of minoxidil, the stability and permeation studies were done with various concentrations of β-CD and HP-β-CD in the solutions.

Objectives

The aim of this present study was specified into 3 main points as follows.

1. To study the effects of β-CD and HP-β-CD on minoxidil solubility.
2. To study the effects of β-CD and HP-β-CD on stability of minoxidil solutions.
3. To study the effects of β-CD and HP-β-CD on permeation of minoxidil through membranes.