CHAPTER I

INTRODUCTION

Fluconazole is an azole antifungal drug. The antifungal azoles are synthetic compounds with one or more 5-membered rings. The azoles are classified as imidazoles such as miconazole and ketonazole or triazoles such as itraconazole and fluconazole. The antifungal effects of the azoles are targeted primarily at ergosterol, the main sterol in the fungal cell membrane. The azoles inhibit ergosterol synthesis through an interaction with C-14 alpha demethylase, an enzyme dependent on cytochrome P-450 that is necessary for the conversion of lanosterol to ergosterol (Joly, Bolard and Yeni, 1992). The depletion of ergosterol alters membrane fluidity, thereby reducing the activity of membrane - associated enzymes and leading to increased permeability and inhibition of cell growth and replication (Van den Bossche et al., 1983). Other antifungal effects of azoles include the inhibition of endogenous respiration, a toxic interaction with membrane phospholipids, and the inhibition of the morphogenetic transformation of yeasts to the mycelial form (Van den Bossche et al., 1983). For comparison, amphotericin B binds irreversibly to ergosterol, and flucytosine inhibits protein synthesis (Francis and walsh, 1992). Although the interaction of azoles and C-14 alpha demethylase in fungal cells underlies their antifungal activity, the potential for similar interactions in mammalian cells with enzymes dependent on cytochrome P-450 also mediates some of the major toxic effects of the azoles. For example, ketoconazole causes clinically important endocrine abnormalities in humans because it inhibits the cytochrome P-450 enzymes necessary for the synthesis of adrenal and gonadal steroid hormones (Santen et al., 1983). One important distinction between the triazoles and imidazoles is the greater preferential affinity of the former for fungal

as compared with mammalian cytochrome P-450 enzymes (Vanden Bossche, bellens and Cool, 1986).

Fluconazole is active against Cryptococcus neoformans and Cryptococcal meningitis. Fluconazole may also be used to prevent relapse following a primary course of antifungal treatment for acute cryptococcal meningitis. In immunocompromised patients at risk of fungal infections. There was a study, which healthy volunteers after ingestion of fluconazole as capsules and after flushing the mouth for 2 min with the same dose formulated as an oral suspension and swallowing of the drug, reported a higher local level of drug exposure in terms of both higher peak concentrations in saliva and a higher salivary AUC, the fluconazole oral suspension has theoretical advantages over the capsule formulation in the treatment of oropharyngeal candidiasis (Koks et al., 1996). Fluconazole is also available as a sterile solution containing fluconazole 2 mg/ml for intravenous administration (Bernie, Steven and Erwin, 1994).

The patients who can not ingest or swallow tablets. An intravenous fluconazole may be an alternative in this situation but an oral liquid formation was more preferable because it was easier to adjust dosages in patient resulted in increase of patient compliance. In economic the cost was also reduced (Yamreudeewong, Lopez - anaya and Rappaport, 1993 ; Steven, Kowalsky and Dennis, 1991).

Generally, liquid preparations had many problems about hydrolysis, oxidation, reduction, photolysis etc. The stability of fluconazole was investigated by Hunt-Fugate, Hennessey and Kazarian (1993). The solution was analyzed in parallel with unireated one. Fluconazole was treated with acid and heat. The

result showed that the concentration of fluconazole was decreased 15.36-23.99 % Cheryl, Lober and Priscilia (1993) also reported that when fluconazole in water was exposed to ultraviolet light for 72 hours, the concentration of fluconazole was decreased by less than 5% the same as in acidic solution. In the alkaline solution and in the hydrogen peroxide solution the concentration of fluconazole were reduced approximately 14% and 31 %, respectively (Cheryl, Lober and Priscilia, 1993).

There were no report about antioxidants and exposure to daylight on the degradation of fluconazole syrup. Therefore the stability of fluconazole syrups in addition of various kinds of antioxidants in the presence and absence of light were studied.

Objectives

The purposes of this study are the following :

1. to study the effect of daylight on the stability of fluconazole syrups,
2. to study the effect of antioxidants on the stability of fluconazole syrups,
3. to predict shelf life of fluconazole syrup at room temperature.