CHAPTER I

INTRODUCTION

It is well known that other than the physicochemical factors, such as formulation, particle size and porosity, other physical factors, as light, relative humidity and temperature, can also change the properties of drug substances and drug products (Al-Turk et al., 1988; Thoma and Klimek, 1991). The principles of this instability are that the drugs will be lost of potency resulting therapeutic ineffectiveness and that the degradation products will cause adverse reactions or toxicities. Therefore, in formualtion, production, storage and administration of drugs one must concern to prevent the degradation that may occur.

Nifedipine is a potent calcium channel antagonist widely used clinically in treatment of hypertention, arrhythmia and angina pectoris. However, it has a low water solubility, as 11 mg/l (Florey, 1989) and a short elimination half-life of 3.4 hours (Foster et al., 1983). Hence, nifedipine rather has a low plasma concentration which fluctuate markedly following administration of conventional capsule dosage form. Therefore, to improve the therapeutic efficiency of nifedipine, the solubility and half-life must be considered.

There are some reports on the improvement of nifedipine solubility. Solid dispersion of nifedipine with water soluble have been developed (Save and Venkitachalam, 1992). In order to prolong nifedipine action, several nifedipine controlled release products have been introduced, such as nifedipine matrix tablets (Chowdary and Ramesh, 1995; Yan et al., 2000). Among these products microparticles or microspheres are one of the most frequently used techniques, for example, chitosan microparticles (Filipovic-Grcic et al., 1996), Eudragit microparticles (Barkai, Pathak and Benita, 1990), polyvinylpyrrolidone-microcrystalline cellulose microcapsulated with

cellulose acetate (Chowdary and Sankar, 1997) and microspheres from combined carriers between Eudragit and povidone K30 (Sinsuebpol, 1999).

One of the techniques used in microparticles preparation is spray drying. The spray drying technique offers many advantages as it is an expeditious, single-step process and the resultant microparticles have a narrow size distribution. Spray drying is also used to enhance the dissolution rate of poorly soluble drugs. This usually occurs as a result of a polymorphic change from a crystalline form to an amorphous form or a metastable crystalline form (Kai et al., 1996).

Nifedipine is very sensitive to light and undergoes photo-oxidation. The main photodegradation product is nitrosophenylpyridine compound when exposed to daylight and is nitrophenylpyridine compound when exposed to ultraviolet light (Majeed et al., 1987). And the degradation rate is higher in solution form than in solid state (Al-Turk et al., 1988). Therefore, it is important to protect nifedipine from light when handling. However, there are many reports on photodegradation of nifedipine both in solution form (Pietta, Rava and Biondi, 1981; Majeed et al., 1987; Al-Turk et al., 1989) and in solid state (Matsuda, Teraoka and Sugimoto, 1989), only few of them is on photodegradation of nifedipine in dosage form (Hayase et al., 1994).

In order to protect nifedipine from photodegradation, the ultraviolet absorbers, or colorants, were used. There are some reports on photoprotection of nifedipine by curcumin (Tonnesen and Karlsen, 1988; Kunchandy and Rao, 1990; Suresh and Prasad,1999).

This study focused on the effects of physical factors, i.e., light and relative humidity and the effects of physicochemical factors, as particle size, formulation and the addition of ultraviolet absorbers and antioxidants on the stability of solid-state spray dried controlled release microspheres of nifedipine with Eudragit RS100 and

polyvinylpyrrolidone K30 (PVP K30). These two polymers were selected as carriers in this study since they are well accepted as nontoxic carriers which are extensively used in the pharmaceutical area.

Objectives

1) To investigate the effects of Eudragit RS100 : PVP K30 mixing ratio, nifedipine : polymers ratio, particle size, spray dry inlet air temperature and light intensity on photostability of nifedipine microspheres.

2) To investigate the effects of addition of some ultraviolet absorbers, e.g., tartrazine and curcumin, on protection of nifedipine in both solution and solid form from photodegradation.

3) To investigate the effect of relative humidity on physical and chemical stabilities of nifedipine microspheres.

4) To investigate the combination effects of light, relative humidity and temperature in ambient atmosphere on chemical stability of nifedipine microspheres.

5) To study degradation kinetics of nifedipine in microspheres.