CHAPTER I

INTRODUCTION

Nifedipine is one of the most potent calcium antagonists in clinical use for angina pectoris, arrhythmia and hypertension. It is highly crystalline and poorly soluble in water (11 mcg/ml at 37°C in distilled water). Its absorption is dissolution rate dependent and low when administred orally in solid dosage forms (Kohri et al., 1987). On the other hand, nifedipine has a short elimination half-life leading to rather low plasma concentration which fluctuate markedly following administration of conventional capsule form of nifedipine (Foster et al., 1983). It is, therefore, important to improve the therapeutic efficiency of nifedipine.

Many nifedipine products have been developed. There were a few report on the formulation of nifedipine controlled release products employing coated granules and matrix tablets (Chowdary and Ramesh, 1995). Several formulation have also been explored: hydroxypropyl-β-cydodextrin/hydroxypropylcellulose double layer tablets (Wang et al., 1993), alginate gel beads, poly (DL-lactide-co-glycolide) (PLGA) microspheres, albumin microspheres (Chauo et al., 1996), chitosan microparticles (Filipovic-Grcic et al., 1996), Eudragit microparticles (Barkai, Pathaka and Benita, 1990 ; Chowdary and Sanke, 1997), ethylcellulose / hydroxypropylcellulose (EC/HPC)

or ethylcellulose / hydroxypropylmethylcellulose (EC / HPMC) microspheres (Guyot and Fawaz, 1998) and polyvinylpyrrolidone-microcrystalline cellulose (PVP-MCC), hydroxypropylcellulose-microcrystalline cellulose (HPC-MCC) microencapsulated with cellulose acetate and hydroxypropylmethylcellulose-microcrystalline cellulose (HPMC-MCC) microencapsulated with Eudragit RLPM (Chowdary and Ramesh, 1995 ; Chowdary and Sankar, 1997).

Spray drying technique is widely used in the pharmaceutical, chemical and food industries. In the pharmaceutical field, it is used in the preparation of spherical particles of drugs and excipients; and in granulating, microencapsulation, complex formation, solid dispersion and drug-drug complex formation (Broadhead et al., 1992). Spray drying is also used to enhance the dissolution rate of poorly soluble drugs (Kai et al., 1996; Yano et al., 1997). This usually occurs as a result of a polymorphic change from a crystalline form to an amorphous form or a metastable crystalline form.

The technique of spray drying offers many advantages; it is an expeditious, single-step process, and the resultant microparticles have a narrow size distribution (Wan, Heng and Chia, 1992; Broadhead et al., 1992; Pavanetto et al., 1992). Spray drying has been used successfully in the preparation of controlled release microparticles made from biodegradable polymers such as polylactic acid (Bodmeier and Chen; 1988; Pavanetto et al., 1993; Conte et al., 1994; Gander et al., 1995), albumin (Pavanetto et al., 1994), chitosan and Eudragits (Takeuchi, Handa and Kawashima, 1989).

The structure of microparticles obtained by spray drying is dependent upon whether the drug is dissolved in or suspended in the coating solution prior to atomization in the drying chamber of the spray drier. When the drug is dissolved in the solution the microparticle has a matrix structure, with the drug being distributed throughout the matrix, but if the drug has been suspended in the coating solution the drug crystal is coated with the coating polymer giving a microcapsule.

Eudragit RS and Eudragit RL (Ammonio Methacrylate Copolymer USP/NF) are biocompatible copolymers of polyethylacrylate methylmethacrylate and trimethylammonioethylmethacrylate chloride. These polymers are inert to the digestive tract content, pH independent, and capable of swelling. The RS type of polymer is less permeable to gastric juice than the RL type due to its lower content in quaternary ammonium functions (RS 1/40 ammonium / ester; RL 1/20 ammonium / ester). Pharmaceutically, Eudragit acrylic resins have been used to formulate oral controlled release delivery systems by coating small particles and matrix tablets, by addition to direct compression tablet (Cameron and McGinity, 1987), microencapsulation of drugs, microparticles of drugs (Kristmundsdottir et al., 1996; Jenquin and McGinity, 1994) and microspheres of drugs (Akbuga, 1991).

Several carriers have been used to enhance the dissolution behavior, polyvinylpyrrolidone or povidone (PVP) is one of popular water soluble polymers, extensively used to enhance and control dissolution rate (Sugimoto et al., 1980 ; Chowdary and Ramesh, 1995).

This study focused on the preparation of microspheres of nifedipine and combined carriers between Eudragit and povidone K30 by spray drying technique. The effect of types of carriers, proportion of combined carriers, concentration of spraying solution and inlet temperatures were investigated. Eudragit RS and RL and PVP K30 were selected as carriers in this study since they are well accepted as nontoxic carriers which extensively used in the pharmaceutical area. The controlled release characteristics of nifedipine microspheres were investigated and release mechanisms were in depth elucidated.

Objectives

The purposes of this study were as follows :

1. To study the preparation of nifedipine microspheres in combined carriers between Eudragit and Povidone K30 by spray drying technique.

2. To investigate the effects of types and combined ratios of carriers on nifedipine release characteristics.

3. To investigate the effects of inlet temperature and concentration of spraying solution in the spray drying process on nifedipine release characteristics.

4. To characterize the physicochemical properties of nifedipine microspheres, e.g., morphology, size and size distribution, X-ray diffraction patterns, differential scanning calorimetric thermograms and infrared spectra. The controlled release mechanisms of nifedipine from microspheres were elucidated.