CHAPTER I

INTRODUCTION

Nifedipine, a highly active calcium channel blocker, is used in the treatment of angina pectoris and hypertension (Reynold, 1989). However, nifedipine is only slightly water soluble (11μg/ml at 37°C) as a result of which the drug may exhibit poor absorption characteristics and bioavailability, after oral administration.

Fincher (1968) reported that rate limiting step of gastrointestinal absorption of nifedipine is the dissolution rate. Therefore, the improvement of nifedipine dissolution from its oral solid dosage forms is an important issue for enhancing its bioavailability and therapeutic efficiency.

Various strategies have been conducted in order to increase nifedipine dissolution; of which is the use of solid dispersions. Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting, solvent, or melting-solvent methods (Chiou and Riegelman, 1971a).

The formation of amorphous forms to increase drug solubility, reduction of particle size to expand the surface area for dissolution, and a decrease in interfacial tension with the aid of water soluble carriers are among the possible mechanisms for increasing dissolution rate, and improving the bioavailability. (Abdou, 1989).

Even though dissolution of drug from solid dispersion depends on the method employed to prepare the dispersion, the proportion and properties of the carrier used should be concerned. Several carriers have been used to enhance the dissolution behavior, polyethylene glycols (PEG) are popular water soluble polymers, extensively used to enhance nifedipine dissolution rate.(Law et al, 1992, Save and Venkitachalam, 1992, Suzuki and Sunada, 1997 and Suzuki and Sunada, 1998)

Cyclodextrins, commonly used for inclusion complex, have been proven to attain positive outcomes when used as a carrier for solid dispersions. Two keys of cyclodextrins are β-cyclodextrin and 2- hydroxypropyl-β-cyclodextrin. There are a number of studies have been published on applications of cyclodextrins in nifedipine solid dispersion systems (Acarturk, Kislal and Celebi,1992 and Hirayama, Wang and Uekema,1994).

Another carrier of interest is poloxamers. Some poloxamers were found to inhibit crystal growth and change crystal habit hence improve dissolution rate (Reddy, Khalil and Gouda, 1976, Luhtala, 1992 and Mackella et al.,1994). Thus, it's interesting to investigate this group of carrier in this study.

An investigation of physicochemical properties of the nifedipine solid dispersion systems would gain the understanding of the mechanisms that enhance drug dissolution. This would allow the prediction for the other poorly soluble drugs.

This study will focus on the nifedipine-carrier solid dispersion system in depth to elucidate the specific mechanism involving dissolution enhancement. The preparation by melting, solvent and kneading methods, the proportion and types of carriers are investigated. PEGs, poloxamers and cyclodextrins are

selected as carriers in this experiment. These carriers are well accepted as nontoxic carriers which extensively used in the pharmaceutical areas.

Objectives.

The purposes of this study are as follows:

1.To prepare nifedipine solid dispersions by melting, solvent and kneading methods.

2. To investigate the effects of types of carriers, mixing ratio between drug and carrier and preparation methods on dissolution of nifedipine compared to their corresponding physical mixtures.

3. To examine the characteristics of the obtained solid dispersions by infrared absorption spectroscopy (IR), differential scanning calorimetry (DSC), powder X-ray diffractometry and scanning electron microscopy (SEM).

4. To elucidate the mechanism(s) of enhanced dissolution of nifedipine solid dispersions.