CHAPTER I

INTRODUCTION AND LITERATURE REVIEW

Gastrointestinal absorption and bioavailability of hydrophobic drugs are usually limited by their poor solubility and low dissolution rate (1). Solid dispersion has been used to improve these parameters.

Terminology

The most widely used definition of solid dispersions is that put forward by Chiou and Reigelmans in 1971 (2). They are dispersions of one or more very slightly soluble active ingredients in one or more water-soluble inert excipients (2-4). The inert excipients which were widely used as carriers in solid dispersion preparations are polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), urea, etc.

Methods of Preparation

Solid dispersions can be obtained by three procedures: by melting, by using solvents, or by a combined process including melting and solvents.

Sekiguchi and Obi first used the melting method in 1961 (2). It consisted of melting the physical mixture of a drug and a water-soluble carrier by agitation and then, by cooling. This caused a rapid solidification of the obtained liquid mixture. The

product is then crushed, pulverized, and sieved. This is the melt.

The solvent method was used for the first time by Tachibana and Nakamura in 1965 (3). This consisted of dissolving a drug and a carrier in an organic solvent which was then evaporated. The product obtained is crushed, pulverized, and sieved. This is the coprecipitate. This method does not involve the risk of decomposition or evaporation of the component products by heat. However, a certain number of drawbacks subsist: the choice of the solvent, the difficulty of its complete elimination and, finally, the highly cost of the process.

Mechanisms of Increased Dissolution Rates (2,3,5)

The enhancements of dissolution by solid dispersions included: a solubilizing effect by the carrier, a decreased particle size of drug within the dispersion, a decreased in aggregation and agglomeration in hydrophobic drugs, an increased wettability, a formation of soluble compound or complex between drug and carrier, and a solidification of the drug in a metastable or amorphous form which is readily available for rapid dissolution. It is probable that any of these factors, or any combination might contribute to the increase in the dissolution.

Physicochemical Structures of Solid Dispersions (2,3)

The physicochemical structures of solid dispersions play an important role in controlling their drug release. Six representative structures: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitations in a crystalline carrier, compound or complex formation, and

combinations, have been outlined to represent the interactions between the drug and carrier.

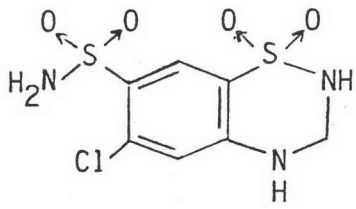
Many available methods contribute to the information regarding the physical nature of a solid dispersion system are thermal analysis, X-ray diffraction, microscopic, spectroscopic, thermodynamic, and dissolution. Because of the different sensitivities, advantages and disadvantages of each method, a combination of two or more methods is required for complete interpretation.

Aging of Solid Dispersions

Since many dispersions contain amorphous or molecularly dispersed drugs, the fast release characteristics of drugs in solid dispersion systems are often affected by aging or storage under various conditions. Aging effects that are manifested as followed: coarsening of eutectic mixtures (6), precipitation from solid solutions or glass solutions (2,3), and polymorphic transformations (7), may lead to changes in the dissolution rates.

Solid dispersions are temperature and very moisture sensitive (7-10) because chosen carriers are usually hygroscopic. Dissolution rate of many dispersions decreased under high humidity conditions (7,8,10). However, unchanged or increased dissolution rates were obtained from some dispersions (3,11-13).

Hydrochlorothiazide



Hydrochlorothiazide (HCTZ) is a member of the benzothiadiazine class of orally effective diuretics widely used in the treatment of hypertension, congestive heart failure, and other edematous conditions. As a class, these compounds generally are poorly wetted and have limited solubilities (14) (see Appendix A). They have been identified as a class of drugs with a potential for bioequivalency and bioavailability problems (15-16). A dissolution requirement appears in the USP-NF (17). Dissolution and bioavailability of HCTZ dosage forms have been reported as formulation dependent (18-21). Significant *in vitro* dissolution test and *in vivo* urine excretion correlations was found (20-22). Additionally, low HCTZ bioavailability is believed to be related to poor product dissolution characteristics (20, 22).

The use of solid dispersion technique in improving dissolution and bioavailability of HCTZ was previous reported (23-26). Various carriers, in high ratios, were used to produce fast dissolution rate solid dispersions. The preparation of solid dispersions appeared to be a useful technique for overcoming the undesirable properties of HCTZ. However, extensive experimental data regarding physicochemical properties of such dispersed systems

containing HCTZ have not been reported.

The objectives of the present study are:

1. To prepare solid dispersions of HCTZ in various carriers using both melting and solvent methods.

2. To investigate the influence of the types and the fraction of carriers on the dissolution of HCTZ from solid dispersions.

3. To select the carrier of choice and its appropriate fraction for increasing dissolution rate of HCTZ from solid dispersions.

4. To compare the results obtained from both methods and determine which method is better.

5. To evaluate mechanisms of increased dissolution rate of HCTZ from solid dispersions.

6. To evaluate aging effect on chemical stability and dissolution rate of HCTZ from solid dispersions.