CHAPTER I

INTRODUCTION

Solid dispersion technique has been used widely in increasing dissolution rates of poorly water soluble drugs (Chiou and Reigelman, 1971). In solid dispersion systems an insoluble drug is dispersed in an inert soluble matrix. The dispersion of a drug within a water-soluble carrier effectively causes a reduction in particle size of the dispersed drug. Upon exposure to the dissolution medium, the carrier dissolves rapidly and the finely dispersed particles are released with optimum properties for dissolution. In contrast if the drug is dispersed in an inert insoluble matrix the drug release will be retarded. The latter phenomenon leads to the development of oral sustained release pharmaceutical products. Ford (1986) reported the use of methacrylic acid copolymer (Eudragit) as insoluble carriers in preparation of codeine solid dispersion which subsequently being formulated into codeine sustained release tablets. Florence, Haq, and Loveless (1976) demonstrated that solid dispersion of trifluoperazine in polymethacrylate or poly DL-aspartic acid resulted in sustained release of the drug. Waxes such as carnauba wax and castor wax were also employed as carriers in preparing sustained release solid dispersions (Dukkuri, Schroeder, and Deluca, 1978). Shaikh, Abidi, and Block (1987) utilized ethylcelluse of different viscosity grades as carriers in preparation of acetaminophen and theophylline sustained release solid dispersions.

Single and combined soluble carriers have been used as carrier systems for solid dispersion. For increasing dissolution rates of poorly soluble drugs, the combined water-soluble carrier systems were reported to be better carrier systems for solid dispersions than the single water-soluble carrier system (Dangprasirt and Ritthidej, 1989; Miralles, McGinity, and Martin, 1982; Ritthidej and Dangprasirt, 1987).

The use of hydrophilic or swellable polymer in matrix tablet is an alternative way to control drug release. By this technique the tablets containing the drug and a hydrophilic or swellable polymer are produced. When these tablets contact water, rapid hydration of the macromolecules in the solid-liquid interface followed by formation of a viscous layer will cause slow release of the drug. Alderman (1984) studied the roles of cellulose ethers, including Methocel E4M and Carbopol 934P, as swellable hydrophilic matrices for sustaining the release rates of several drugs. Basically,the matrix tablets also can be formulated by mixing the drug with acrylic resins and then being compressed into tablets. The compacting pressure will cause agglomeration of acrylate particles into coherent matrix which will release the drug slowly by diffusion through the matrix pores or by erosion of the matrix. The required amount of dry polymer depends on the drug solubility and the required release profile (Lachman et al., 1983).

Thus it is interesting to investigate the use of insoluble polymer and swellable polymer as combined carriers in retarding drug release in order to yield the controlled release solid dispersion system which hopefully will result in the better control of drug release than the use of either polymer alone. This anticipation bases on the combination of two

mechanisms in controlling drug release, diffusion of drug through insoluble carrier (Shaikh, 1987) and dissolution retarding effect of high viscosity resulting from swelling of swellable polymer in dissolution medium (Alderman, 1984). Therefore the release of drug from the resulting solid dispersion will be controlled by diffusion of drug through insoluble polymer and through viscous environment.

In general the presence of drug in solid dispersion can occur in many forms. These forms include; amorphous form, polymorphic form, complex of drug and carrier, eutectic mixture of drug and carrier, glass dispersion, molecular dispersion, and colloidal dispersion (Chiou and Reigelman, 1971). Drug dissolution from the solid dispersion was influenced by these various forms of drug especially in the case of dissolution rate enhancement. However, in the case of dissolution rate retardation, other than diffusion of drug through the carrier, only complexation of drug and insoluble carrier would be the factor.

Recently, the application of optimization in pharmaceutical research has been recognized. By optimization one can established mathematical models representing the relationships between independent variables and dependent variables (Armstrong and James, 1990). In pharmaceutical research the independent variables consist of formulation or processing variables which are controllable while the dependent variables are the properties of products being manufactured in quantitative terms. Such relationships can be established accurately by the application of suitable statistical experimental designs. The validation of the relationships can be evaluated by statistical analysis. There are many types of statistical experimental designs such as factorial design,

Hadamard matrix, central composite design (Armstrong and James, 1990; Montgomery, 1991; Romero et al., 1989). The selection of a suitable design depends on the nature of the relationship to be established. In the case of linear relationship a simple experimental design such as two-level factorial design or Hadamard matrix can be selected. However if nonlinear relationship is searched the design of more complicated such as three-level factorial design or central composite design should be chosen (Montgemery, 1991). The statistical experimental design is necessary for optimization strategy since by the design the entire area of study will be covered and the effect of each independent variable can be distinguished.

Romero et al. (1989) employed an Hadamard matrix as an experimental design in developmentd of a sustained release formulation. This design was also used in identification of the suitable storage condition of parenteral nutrition (Ozil and Rochat, 1988). By this design only eight experiments are needed in order to establish a linear relationship between four independent variables and a dependent variable or response. Schwartz, Flamholz, and Press (1973) applied a central composite design as an experimental design in constructing nonlinear realtionships between various tablet properties and five independent variables having influenced on tablet production. Such relationships were then utilized in searching for optimum levels of the independent variables which would yield the tablets of required properties. Normally the relationships between independent variables and any dependent variable can by calculated conveniently by the aid of a statistical computer program.

Since the use of spray drying in preparing controlled release solid dispersion is considered as a new application of spray drying. And the use of insoluble carrier and swellable carrier as combined carriers in controlling drug release has never been studied before. Therefore this investigation offers a new trend in development of controlled release drug having the advantage of the convenience in preparing solid dispersion arriving from the use of spray drying. In addition, the use of combined carriers resulted in decreasing the amount of the carriers needed in preparing the controlled release solid dispersion and consequently the development of controlled release dosage form having suitable dosage size can be achieved.

In this investigation optimization method was applied in order to perform the study in systematical and efficient way by using small numbers of experiment. In the past the use of optimization method in pharmaceutical field is limited to personnels with knowledge in computer programming. Thus in this investigation the optimization was done by using commercially available softwares and hence allowing the personnels who lack knowledge in computer programming be able to use optimization in performing their researches effectively.

In the present study diclofenac sodium was chosen as a model drug for development of controlled release solid dispersion systems since it dissolves in ethanol which is the widely-used solvent being utilized in preparing solid dispersion by coprecipitation method. The swellable polymers being utilized in this study were hydroxypropyl methylcellulose (Methocel E4M), carbomer (Carbopol 934), and chitosan while the

insoluble polymers being chosen were methacrylic acid copolymer (Eudragit RS 100) and ethylcellulose (Ethocel 10 cps).

For practical purpose spray drying was applied in preparation of the solid dispersion system by coprecipitation. By spray drying, the solid dispersion can be prepared easily and continuously with rapid rate of production. In addition the spray-dried solid dispersion consists of fine powder which is ready to be developed into capsule or tablet dosage form. For the benefit of pharmaceutical industry, further study on development of optimum controlled release tablets from the optimum spray-dried solid dispersion was conducted.

The first stage of this investigation involved with selection the suitable type of insoluble and swellable polymers to be utilized as combined carriers. In the next stage the effects of various variables having influences on the dissolution characteristics of the prepared diclofenac sodium solid dispersions were investigated. A suitable statistical experimental design, an Hadamard matrix, was used in this stage. The development of diclofenac sodium solid dispersion having the required optimum dissolution profile was then performed utilizing optimization method. This method was reviewed comprehensively by Gould (1984). The last stage of this study concerned about formulation of the diclofenac sodium controlled release solid dispersion into tablet dosage form by direct compression. A statistical experimental design named central composite design and the optimization strategy were applied in order to search for the required tablet formulation which would result in the optimum diclofenac sodium controlled release tablets having the required tablet properties.

The study on mechanism of drug release from the controlled release solid dispersions was performed by scanning electron microscope, differential thermal analysis, and X-ray diffraction in order to investigate the completeness of solid dispersion formation and the form of diclofenac sodium presented in the optimized solid dispersion.

The objectives of the investigation were to:

1. Study the application of spray drying in preparation of diclofenac sodium controlled release solid dispersions utilizing methacrylic acid copolymer (Eudragit RS 100) and ethylcellulose (Ethocel 10 cps) as insoluble carriers and hydroxypropyl methycellulose (Methocel E4M), carbomer (Carbopol 934), and chitosan as swellable carriers.

2. Select a suitable insoluble carrier and a suitable swellable carrier in order to be employed as combined carriers in preparation of diclofenac sodium controlled release solid dispersion by spray drying.

3. Compare the influences of single carriers and combined carriers on the drug release characteristics and rates from diclofenac sodium solid dispersions.

4. Optimize the preparation of diclofenac sodium controlled release solid dispersion in order to yield the solid dispersion system of optimum drug release characteristic and rate by using optimization method.

5. Optimize the manufacture of diclofenac sodium controlled release tablets prepared from the optimized diclofenac sodium controlled release solid dispersion in order to yield the controlled release tablet of optimum tablet properties including drug release characteristic and rate by using optimization method.

6. Study the application of commercially available statistical computer programs in optimization strategy in order to establish the relationships, both linear and nonlinear, between various independent variables and the experimental responses. From these relationships the required optimum responses can be predicted.

7. Study the mechanism of drug release from the optimized diclofenac sodium controlled release solid dispersion.