CHAPTER V

CONCLUSION

In this investigation the diclofenac sodium controlled release powder was developed by solid dispersion technique using spray drying. By the help of an appropriate statistical experimental design, an Hadamard matrix H[8], the optimization strategy was applied in order to obtain the optimum diclofenac sodium controlled release solid dispersion imparting the optimum drug release profile. The application of the Hadamard matrix in the first stage of this study was possible due to the simplification of the powder system of diclofenac sodium controlled release solid dispersion. Therefore linear relationships between the studied responses and the investigated independent variables could be established. However, the more complex situation existed in the next stage of the investigation. In this stage the development of diclofenac sodium controlled release tablets from the optimum diclofenac sodium controlled release solid dispersion powder was processed. The development of an optimum tablet formualtion was more complicated since the effects of various factors on the studied responses were not simple and the linear relationships between the responses and the independent variables might not valid enough. The expectation of nonlinear relationships therefore required the utilization of a central composite design which was appropriate for establishing a second-order model of nonlinear relationship.

The linear relationships were shown to fit well to the system of diclofenac sodium controlled release solid dispersion powders. While the non-linear relationships were proven to valid in the system of diclofenac sodium controlled release solid dispersion tablets. Regardless of linear or non-linear model the surface plot and contour plot were the effective tools in locating the optimum conditions which would result in a required response. The validity of the model being established was confirmed by statistical analysis of the obtained t-values or partial F-values. However, the investigator must aware that the obtained relationships were valid for the independent variables only in the range of the levels that being studied.

For the development of diclofenac sodium controlled release solid dispersion powder, the most important parameter imparting the significant influence on drug release profile was the absolute ethanol proportion. Increasing the ethanol proportion of the spray feeding liquid caused more retardation and consistence of drug dissolution. Higher amount of ethylcellulose and chitosan in the feeding liquid also resulted in slower drug release. The amount of ethycellulose was the most prominent factor in controlling consistency of drug release, increasing ethylcellulose content caused more consistence in drug release characteristic. An optimum set of conditions for preparing spray-dried diclofenac sodium controlled release solid dispersion powder, containing 10 g of drug, were spray feeding volume of 200 ml, absolute ethanol proportion of 0.7, ethylcellulose content of 2.5 g, and chitosan content of 0.02 g.

For the development of diclofenac sodium controlled release solid dispersion tablets, the response of interest was proven to be drug release characteristic. Other tablet properties including tablet weight variation, friability, hardness, and disintegration time were shown to be acceptable in the range of the levels of the independent variables being studied. The most important parameter affecting drug dissolution profile of diclofenac sodium controlled release solid dispersion tablets was the amount of the disintegrant, Ac-Di-Sol, being utilized in the tablet formulation. Increasing the amount of Ac-Di-Sol caused faster and less consistence in drug dissolution. The interaction between Era-Tab and Ac-Di-Sol also imparted significant effect on drug dissolution. Other parameters having effect on consistency of drug release were compression force, interaction between Era-Tab content and Ac-Di-Sol content, and squared-term effects of compression force and Era-Tab content. These effects were complicated thus the nonlinear relationships were existed and the model became second-order model. The central composite design was shown to be useful as the screening tool to approximately locate the optimum conditions of the independent variables. However, a further stage of experiment was needed in order to locate these optimum conditions more precisely. An optimum condition in preparing diclofenac sodium controlled release solid dispersion tablet, containing 100 mg of drug, was found to be compression force of 700 psi, Era-Tab content of 194.8 mg per tablet, Ac-Di-Sol content of 6.4 mg per tablet, and magnesium sterate content of 1.6 mg per tablet.

The dissolution profiles of the optimum diclofenac sodium controlled release tablet and powder were similar. Their experimental dissolution profiles lied almost completely within the 99% confidence

band of their predicted dissolution profiles. Drug release from the optimized diclofenac sodium controlled release powder and tablet were demonstrated to be diffusion controlled. High alcoholic content in the spray feeding liquid was important for solid dispersion formation and hence controlled drug release. In the optimized diclofenac sodium solid dispersion, the drug was dispersed in the polymer matrix as amorphous form or as molecular level. Diffusion of the drug through ethylcellulose, an insoluble polymer, and through viscous environment produced by chitosan, a swellable polymer, were beleived to be the controlled release mechanisms.

The application of solid dispesion utilizing combined carriers in the field of controlled release drug delivery system was proven to be possible. The use of combined-carriers system also imparts some advantages over the use of single carrier system. These advantages include reduction in the size of the tablets since less amount of carriers are employed and less stickiness of the obtained solid dispersion due to lower content of carriers being used. Spray drying technique was shown to be successful in preparing controlled release solid dispersion powder. However, the bulkiness of the obtained spray-dried powder requires careful consideration in selection of the appropriate direct compressible vehicle for tablet manufacturing. Further study on the stability of the optimized diclofenac sodium controlled releasse solid dispersion is suggested since the change from metastable form to a more stable form may occur and if this is the case then the drug release characteristic may change with the time and the method to retard such change must be searched.