CHAPTER IV

DISCUSSION AND CONCLUSIONS

Pure and treated ergoloid mesylate powder exhibited poor dissolution in 0.1 N.HCl owing to its hydrophobicity and occurence of clumping together of the drug particles in the dissolution medium. This could diminish the surface area available for dissolution (Law and Chiang, 1990). Ergoloid mesylate incorporated in solid dispersions with PVP, PEG or poloxamer 188 displayed higher dissolution rates than the corresponding physical mixture, pure drug, and treated drug.

X-Ray Diffraction Studies

The absence of crystalline ergoloid mesylate peaks were observed from X-ray diffraction patterns in every solid dispersion system (Figures 78-83). This might indicate that ergoloid mesylate might be present as an amorphous form in ergoloid mesylate-carrier(s) system. The absence of apparent crystalline peaks might be caused by an extremely fine dispersion of ergoloid mesylate in the solid dispersion system.

DTA Studies

DTA thermograms of all solid dispersion systems (Figures 72-77) were interpreted. The thermograms of ergoloid mesylate-carriers solid dispersions showed only carriers endotherm peak, no endotherm peak of ergoloid mesylate were found. It displayed some interaction between ergoloid mesylate and carrier. Since no

new peaks were observed in the thermogram, it is not chemical interaction. In physical mixture, the thermogram was the combined features of thermograms of each component, also indicated no interaction. But some endotherm of drug was absence, it may be low concentration of drug.

IR Absorption Studies

For all solid dispersion system, the IR absorption (Figures 66-71) characteristic of ergoloid mesylate was typical, except a few low scattering peaks were observed in some systems. Consequently, there was no chemical interaction. However, there was some interaction between ergoloid mesylate and carriers. This might due to the amorphous form of ergoloid mesylate. In physical mixture, they revealed no interaction between ergoloid mesylate and carriers since no new peaks were observed and none of the sharp bands in the dispersion systems disappeared.

In the mixture of 3% poloxamer 188 in PVP K-30 solid dispersion system the peaks of O-H stretching of ergoloid mesylate at 3400 $cm.^{-1}$ and C=O stretching of six-member ring ergoloid mesylate at 1700 $cm.^{-1}$ showed smaller peaks than its physical mixture system. It can be explained that OH group formed the intermolecular hydrogen bonding with C=O group of six member ring ergoloid mesylate.

SEM Studies

Examining the SEM photomicrographs, the well defined needle shape of pure drug particles turned into coarse particles after the drug was treated. The dissolution profile increased

very slightly, this might due to the clumping together of the drug particles in the medium. Solid dispersion of ergoloid mesylate and carrier(s) homogeneously mixed together in such a degree that ergoloid mesylate particles might increase dissolution which could be explained as follows:

1. The carrier might act as protective colloid in retarding coaggulation, aggregation or coarsening of the fine crystallites before solidification (Chiou and Riegelman, 1971).

2. Coevaporation of drug and carriers might result in the formation of fine particles, hence the specific surface area of drug particles might increase and so did the dissolution rate.

3. A possible solubilization effect by the carrier in the microenviroment (diffusion layer) immediately surrounded the drug particle.

4. Wetting characteristic and dispersibility of drug powder in the carrier, etc.

Solid dispersions of ergoloid mesylate with various carriers of different molecular weights and various ergoloid mesylate-carrier(s) ratios were studied. The most effective carrier with the optimum ergoloid mesylate-carrier(s) ratio that exhibited the good dissolution behaviors and mechanisms of enhanced dissolution of ergoloid mesylate were selected.

Ergoloid mesylate - PVP Dispersion Systems

Since PVP of various molecular weights are commercially available, it is important to determine whether behavioral differences exist with a variation in polymer chain length. Illustration of various molecular weight of PVP is shown in Appendix 21 (Doherty and York, 1987).

Two different molecular weights of PVP as carriers were selected in the preparation of ergoloid mesylate solid dispersions. The PVP K-30 systems increased the dissolution of ergoloid mesylate higher than PVP K-90 systems (at the same weight fraction). In general, dissolution of drug decreased as the molecular weight of carrier increased (Ford, 1986). The increase in molecular weight of PVP resulted in an increased solution viscosity, and retarded drug dissolution profile (Doherty and York, 1987).

Due to many similar physical properties between the PEG and PVP polymers, it was believed that the theoretical model of PEG may provide a possible qualitative explanation to this interesting phenomenon (Chiou and Smith, 1971). It was shown that the molecular weight was an important determinant of PEG dissolution rate, the decrease in dissolution rate with increasing molecular weight corresponded with a decrease in diffusion coefficients. An empirical relationship between molecular weight and dissolution rate of the form (Corrigan, 1986)

$$G = KM^{-A}$$

where G = the dissolution rate

M = the molecular weight

K and A = constants proposed for polymer

Dissolution profiles of ergoloid mesylate-PVP solid dispersions dissolution and physical mixture increased with increasing PVP weight fraction. This may be attributed to the fact that the amount of carrier used did not reach their optimum solubilizing effect, therefore further increase in the amount of carriers could markedly increase the ergoloid mesylate dissolution rate. However, carrier might increased medium viscosity around the drug particle. This effect would reduce the dissolution rate of ergoloid mesylate in the diffusion layer and hence retard the dissolution rate.

Comparison of the results of dissolution obtained for solid dispersions systems with those for physical mixture showed that, at all weight fractions, the former gave higher dissolution rate. This may due to the molecular dispersion of drug in PVP matrix, which accounts for the increased surface area and hence faster dissolution. Moreover, X-ray diffraction studies indicated an amorphous form of ergoloid mesylate in solid dispersions with PVP.

Ergoloid mesylate - PEG Dispersion Systems

The higher dissolution rate of drug with this system than pure drug may be attributed to the presence of PEG, by reducing the surface tension of the medium. Other factors such as increased wettability, reduction or absence of aggregation and agglomeration and solubilization of drug by the carrier at the diffusion layer of particles may also partially contribute to the enhancement of dissolution of ergoloid mesylate-PEG dispersed systems (Chiou, 1977).

Since there are many grades of PEG available, PEG 4000, and PEG 6000 were selected, to compound with various quantity of ergoloid mesylate, to determine the effect of molecular weight and weight fraction of PEG on dissolution of ergoloid mesylate. Different degrees of dissolution rate enhancement achieved by PEG 4000 and PEG 6000 were found and appeared to depend on the molecular weight of the polymer. The degree of dissolution rate enhancement decrease as the molecular weight of PEG increased. These results may be explained by the increase of viscosity of diffusion layer of ergoloid mesylate, thus retarded dissolution of the drug as previously discussed in PVP dispersion system. Using an empircal relationship between molecular weight and dissolution rate as discussed previously in PVP system, the PEG dissolution rate (G_{PEG}) and molecular weight data may be related by

$$G_{PEG} = 4.623 * 10^4 M^{-0.52}$$

where M is the molecular weight (Corrigan, 1986)

Varying the amount of carriers used (1:1, 1:3, 1:5, and 1:7 ratios of drug:PEG) in preparation of ergoloid mesylate solid dispersions in both PEG 4000, and PEG 6000 system, difference in the dissolution of ergoloid mesylate from solid dispersions were found. The degree of dissolution rate enhancement achieved by PEG increased as the weight fraction of PEG increased. It was shown to be the balance between the dissolution-promoting effect of increasing drug solubility due to solubilizing effect of PEG and the viscosity-related retarding effect of increasing PEG concentrations in diffusion layer. The results indicated that the dissolution-promoting effect was greater than the viscosity-ralated retarding effect.

The X-ray diffraction spectra indicated that ergoloid mesylate was present in an extremely fine dispersion, possibly in amorphous form by absence of crystalline peak, in solid dispersion systems. Thus the enhanced dissolution of the ergoloid mesylate solid dispersions could be due to its presence in amorphous state, as a high energy polymorph.

Ergoloid mesylate - Poloxamer 188 Systems

Poloxamer 188, a nonionic surfactant, increased the dissolution rate of drug by increasing wettability ability of the powder, presumably by lowering the interfacial tension, such effect may also operate significantly in the microenviroment (diffusion layer) immediately surrounding the drug particles, especially in the early stage of dissolution from solid dispersed forms, since the carrier would completely dissolve in a short

period of time. Other reasons might be due to micellar solubilization (Chiou and Niazi, 1971; Reddy, Khalil, and Gouda, 1976). Hence, the presence of poloxamer 188 made the dissolution of the drug faster than pure drug.

The absence of X-ray diffraction peaks in solid dispersions indicates that ergoloid mesylate is present in an extremely fine dispersion, possibly in amorphous form. So the dissolution of solid dispersions became faster than physical mixture, at the same ratio. The degree of dissolution enhancement achieved by poloxamer 188 markedly showed increased as the weight fraction increased. This may be due to the molecular level dispersion of drug in poloxamer 188 matrix, which accounts for the increased surface area.

Ergoloid mesylate - 3 % Poloxamer 188 in PVP K-30 System

In mixture of 3 % poloxamer 188 in PVP K-30 systems, both solid dispersions and physical mixture dissolution profiles were superior to PVP K-30 systems but they were inferior to poloxamer 188 systems. It might be due to the better dissolution of poloxamer 188 than PVP K-30, thus dissolution of the mixture systems was between PVP K-30 and poloxamer 188 system. From this investigation, dissolution data of ergoloid mesylate-3 % poloxamer 188 in PVP K-30 solid dispersions increased while weight fraction of carriers increased. It could be explained by the same reasoning of PVP K-30 and poloxamer 188 system as discussed above.

From Figure 46, poloxamer 188 dispersion system and PVP K-30 dispersion system were found to yield the highest and third highest dissolution rate, respectively. Therefore, the poloxamer 188 and PVP K-30 system were chosen for tablets manufacturing trials. The quantity of carrier as least as possible to provide good dissolution and tabletting characteristics were employed in formulation. It was recommended that 3-15 % of PVP would be the optimum quantity in tablet formulation hence drug:carriers at 1:5 ratio was selected in ergoloid mesylate tablets. Additionally, PVP K-30 is widely employed as tablet binding agent in manufacturing. Its dual roles as carrier and binder has advantage over poloxamer 188. Therefore, PVP K-30 was selected as agent of choice in this experiment.

Ergoloid mesylate Tablets

Five commercially available ergoloid mesylate tablet brands were studied. Physical properties of the commercial ergoloid mesylate tablets were found to vary greatly among various brands. This may due to variation in formulation especially the type and quantity of excipients, and manufacturing process. Brand B exhibited the best dissolution released, but yielded high variation in ergoloid mesylate content uniformity. Brand E exhibited satisfactory tablet quality and acceptable dissolution profile. Thus, the prepared ergoloid mesylate tablets, were manufactured to match brand E in physical properties, ie. tablet weight, hardness, thickness, disintigration time, etc.

Content uniformity of the prepared ergoloid mesylate tablets, employing traditional wet granulation method (formula A), modified solid dispersions of wet granulation method (formula B), and traditional direct compresion method (formula C), were within the USP. requirement. While the tablets prepared from solid dispersions of direct compression method (formulae D and E) failed to meet the compendial limit. This may due to the difference in particle sizes between the excipient and drug particles in solid dispersions which led to segregation of drug and diluents during mixing process. Furthermore, the solid dispersion particles using PVP K-30 and poloxamer 188 are highly hygroscopic, caused aggregation of the particles.

Figure 84 summarized the dissolution properties of the prepared tablets. Dissolution rate of tablets prepared using the direct compression technique (formulae C, D, and E) were considerably higher than the rate of wet-granulated method (formulae A and B). This may result from the lower disintegration times and hardness in direct compression formula. Lacking of intergranular bridges of binder (PVP K-30) in direct compression method, the adhesion between particles is weaker than wet granulation method.

The wet granulation formula, formula B possessed higher dissolution rate than formula A while the disintegration time of both formulae showed no difference. The reason for higher dissolution, for formula B, might be ergoloid mesylate had dissolved into PVP and changed to solid dispersions state after drying. But, for formula A, ergoloid mesylate had been dispersed

as particle only. Both formulae were prepared with the same technique and equal quantities of all ingredients. So the both disintegration times should be equal.

For direct compression formulae, formulae D and E exhibited better dissolution profile than formula C. This could be explained in the same manner as previously described. From the dissolution studies of solid dispersion powders, they indicated that the poloxamer 188 solid dispersions exhibited higher dissolution profile than PVP solid dispersions. Base on the results, the dissolution profile of formula D (PVP K-30 dissolution) is nearly equal to its of formula E (poloxamer 188 solid dispersion). One reason was that low concentration of solid dispersions (3.6%) was employed in the formula.

Formula B, modified solid dispersions of wet granulation method, displayed lower dissolution profile than formula D, solid dispersions of direct compression method. One reason, as previously discussed, was the high disintegration time and hardness in formula B. The other might be that the ergoloid mesylate in formula B was entrapped in the excipient granules during the granulating process, so that its dissolution rate was retarded. Base on the resultant tablet properties, it could be concluded that formulae D and E exhibited better dissolution characteristic. Although these formulae showed poor content uniformity, it could be overcome by seiving the dispersion powder into the same particle size as the excipients before incorporating in formulation, in low humidity environment.

Comparing dissolution profile of tablets from formulae D and E with commercially available products, formulae D and E exhibited better dissolution profile than the commercially available products tested except brand B. The dissolution rate of brand B was higher than those of formulae D and E, was due to the brand B's short disintegration time. Consequently, the disintegration time appeared to be the rate determining step for dissolution profile of ergoloid mesylate tablets.

Conclusion

Solid dispersion with various carriers yielded more rapid dissolution of ergoloid mesylate than pure drug and corresponding physical mixtures. The carriers gave faster dissolution characteristics of ergoloid mesylate were ranked as follow: poloxamer 188 > 3% mixture of poloxamer 188 in PVP K-30 > PVP K-30 > PVP K-90 > PEG 4000 > PEG 6000. The dissolution rate of the drug increased as the ratio of carrier to drug was increased. From x-ray diffraction, IR absorption, and DTA studies, an important role in improving the dissolution characteristic of ergoloid mesylate in solid dispersion was the presence of ergoloid mesylate in amorphous, high energy form.

The dissolution profile of the prepared tablets from five procedures were complied with USP requirement. The modified direct compression procedures (formula D, and E) produced the fastest dissolution rate of the drug and exhibited better dissolution profile than the commercial ergoloid mesylate tablet products except brand B.