CHAPTER IV

DISCUSSION AND CONCLUSION

A. Drug-Single Carrier

The presence of dextrose, a water soluble diluent, in prednisolone or indomethacin tablets caused improvement in tablets disintegration times comparing to the prednisolone or indomethacin control tablets. Dextrose, being hydrophilic, would be expected to increase the wettability of the prednisolone and indomethacin particles and hence their dissolutions compared with drugs alone. This hydrophilicity of dextrose was believed to be responsible for the faster dissolution rates of the tablets containing prednisolone-dextrose or indomethacin-dextrose physical mixtures than the prednisolone or indomethacin control tablets.

Dextrose presented in the prednisolone tablets might impart some viscosity around the drug particles. Since the dissolution of prednisolone was reported to be diffusion control (41) therefore the increase in viscosity would reduce the diffusion rate of the drug in the diffusion layer and thereby reduce the dissolution rate. This dissolution retarding effect was believed to more than compensate for the small increase in the solubility of prednisolone, imparted by dextrose, resulting in slower dissolution rate of the tablets containing 1:1 prednisolone:dextrose physical mixture compared to the prednisolone control tablets. The same observation was seen in the first part of dissolution profile of the tablets of 1:1 prednisolone: dextrose coprecipitate.

For the tablets of prednisolone-dextrose or indomethacin-dextrose, the tablets containing coprecipitate showed faster drug dissolution rate than the tablets containing physical mixture having the same ratio of drug:carrier. The enhanced dissolution rate could be attributed to three factors. Firstly dextrose as it dissolved may have a solubilizing effect on the drug. Secondly the particle size of the drugs in coprecipitate would be small causing increase in surface area and hence dissolution rate. Finally in a coprecipitate where each crystallite of drug was surrounded by a water soluble crystal, there would be good wettability and dispersibility of the drug in dissolution medium. Aggregation and agglomeration and lumping in the dissolution medium between pure drug particles are rarely presented in most solid dispersion systems since the individually dispersed particles are surrounded by carrier particles.

Since no significant difference in disintegration times among the tablets containing prednisolone-dextrose coprecipitates was observed. Therefore a conclusion could be made that as the higher amount of dextrose was used as carrier, the faster prednisolone dissolution rate was the result. This finding agrees with the previous report which stated that when the coprecipitation technique was used, the dissolution was found to increase as the carrier content was increased (15). This result may be due to a greater dispersion of prednisolone molecules and hence a greater surface area, and the presence of higher content of dextrose which imparted more wetting and solubilizing effects on prednisolone.

Although the incorporation of prednisolone-dextrose coprecipitate or indomethacin-dextrose coprecipitate into tablets did not present problem but not much enhancement in drug dissolution rate was obtained compared to the tablets of drug-dextrose physical mixture. More dextrose may be needed in order to get more drug dissolution rate enhancement. However, if too high quantity of dextrose is used the problem in compaction will exist. Besides, dextrose is poorly soluble in ethanol (42), the problem of coprecipitation with drug will arise if high amount of dextrose is employed. Dextrose will precipitate out first during evaporation of ethanol and the resulting mass will be the combination of pure drug and drug-dextrose coprecipitate therefore only limit quantity of dextrose should be employed in coprecipitation.

Although the tablets prepared from 1:1 indomethacin:dextrose coprecipitate gave much improvement in indomethacin dissolution rate compared to the indomethacin control tablets. However, those tablets barely miss the USP XXI & NF XVI dissolution requirement for indomethacin solid dosage form (2) since they yielded 79% indomethacin dissolution within 20 minutes while 80% indomethacin dissolution within 20 minutes is required. The more suitable way is to incorporate the coprecipitate into capsule dosage form since the compaction process often destroys the improved dissolution achieved by solid dispersion (43).

PEG 4000 is a crystalline, water-soluble polymer with two parallel helixes in a unit cell. It is predicted that significant amounts of drug can be trapped in the helical interstitial space (12)

thus interstitial solid solution is formed. Viscosity produced by PEG 4000 also helps in formation of metastable solid solution (12). Besides PEG 4000 may also act as protective colloid in retarding the coagulation, aggregation, or coarsening of the fine crystallites before solidification (12).

Indomethacin has been found to form solid solution with PEG 6000 in indomethacin-PEG 6000 solid dispersion prepared by melting method (46). Thus the improvement in prednisolone and indomethacin dissolutions of the tablets containing drug-PEG 4000 coprecipitates was thought to result from the interstitial solid solution between the drugs and PEG 4000 resulting in molecular or colloidal dispersion of drug in PEG 4000.

PEG 4000 also provided solubilizing effect on some hydrophobic drugs (29,39). The solubilizing effect of the carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particle in the early stage of dissolution since the carrier completely dissolves in a short time (12). This solubilizing effect of PEG 4000 on indomethacin resulted in faster dissolution rate of tablets containing 1:1 indomethacin:PEG 4000 physical mixture compared to the indomethacin control tablets.

For the tablets of prednisolone-PEG 4000, the solubilizing effect of PEG 4000 on prednisolone was hindered by the tablet disintegration retarding effect of high amount of PEG 4000 presented in the tablets. However, this solubilizing effect was evident by faster dissolution rate of the tablets containing 1:5 prednisolone:PEG 4000 physical mixture than the tablets containing 1:3 prednisolone:

PEG 4000 physical mixture after the tablets disintegrated completely.

Polyethylene glycol acts as binder on tabletting (43,44). The higher amount of PEG 4000 presented in prednisolone tablets, the slower the tablet disintegration time was obtained. The delaying in tablet disintegration produced by high amount of PEG 4000 in tablets containing 1:5 prednisolone:PEG 4000 or 1:1 indomethacin: PEG 4000 coprecipitate destroyed the improvement in dissolution achieved by coprecipitation. However, when the tablets disintegrated completely the improvement in dissolution of both drugs over the tablets of 1:5 prednisolone:PEG 4000 or 1:1 indomethacin:PEG 4000 physical mixture and the control tablets was obtained.

For 1:1, 1:3, 1:5 prednisolone:PEG 4000 and 1:1 indomethacin :PEG 4000 ratios the tablets of physical mixtures exhibited faster disintegration times than the tablets of coprecipitates. This result may be due to less contact between the drug and PEG 4000 occured in physical mixtures comparing to coprecipitates.

Polyethylene glycols were reported to impart viscosity to the solution (18,45). High viscosity imparted by PEG 4000 was thought to be another factor in retard dissolution rate of prednisolone tablets containing PEG 4000. This effect was seen clearly in the tablets of 1:1 prednisolone:PEG 4000 which showed some slower dissolution rates than the prednisolone control tablets although their average disintegration times were faster than the prednisolone control tablets.

Usually high amount of carrier is required in preparing solid dispersion in order to get significant improvement in drug

dissolution (12). However, when PEG 4000 was used as carrier for prednisolone or indomethacin coprecipitation in high amount, the resulting coprecipitate yielded tablets with slow disintegration time. Therefore, the prednisolone-PEG 4000 and indomethacin-PEG 4000 coprecipitates are not suitable for incorporation into tablet dosage form. The tablets of 1:5 prednisolone:PEG 4000 and the tablets of 1:1 indomethacin:PEG 4000 do not meet the USP dissolution requirements for prednisolone tablets (7) and indomethacin capsules (2) which require the minimum of 60% prednisolone dissolution within 20 minutes and the minimum of 80% indomethacin dissolution within 20 minutes respectively.

SLS is waxy in nature. Higher amount of SLS in tablets yielded tablets with higher disintegration times. For prednisolone tablets containing drug-SLS, increasing amount of SLS from 5 mg per tablet to 25 mg per tablet seemed to produce the comparable dissolution rate enhancement if the effect of disintegration time was excluded. The faster dissolution rates observed from the tablets containing 1:1 prednisolone:SLS compared to the tablets containing 1:3 or 1:5 prednisolone:SLS was believed to result solely from their faster disintegration times.

The faster disintegration time of the tablets containing prednisolone-SLS coprecipitate compared to the tablets containing prednisolone-SLS physical mixture of the same drug:SLS ratio was a reason for their faster dissolution rates.

For indomethacin tablets containing 1:1 indomethacin:SLS, the tablets of coprecipitate exhibited comparable disintegration

time to the tablets of physical mixture. Thus the more improvement in indomethacin dissolution rate occured from the tablets of coprecipitate than from the tablets of physical mixture was due to molecular or colloidal dispersion of indomethacin in SLS.

In drug-SLS coprecipitate, molecules of drug were intimately encircled by SLS thereby the wetting effect of the surfactant SLS on the drug was believed to be higher in coprecipitate than in physical mixture. Therefore the more wetting effect of SLS on drug occured in coprecipitate was the reason for the faster disintegration time obtained from the tablets of prednisolone-SLS or indomethacin-SLS coprecipitate compared to the tablets of prednisolone-SLS or indomethacin-SLS physical mixture having the same ratio of drug:carrier.

When SLS was used in high amount for preparing prednisolone coprecipitates, the low solubility of SLS in ethanol (42) may cause SLS to first precipitate out from the ethanolic solution of prednisolone and SLS during evaporation of ethanol. The resulting mass would be pure SLS and prednisolone-SLS coprecipitates. It was possible that the same quantity of true prednisolone-SLS coprecipitates obtained from 1:1, 1:3, and 1:5 prednisolone:SLS coprecipitates would result from prednisolone and about the same amount of SLS. Thus about the equal quantity of true prednisolone-SLS coprecipitate occured from the 1:1, 1:3, or 1:5 prednisolone:SLS coprecipitation. However, the additional amount of pure SLS would be highest in the tablets of 1:5 prednisolone:SLS coprecipitation and

lowest in the 1:1 prednisolone:SLS coprecipitation, causing slowest disintegration time in the tablets of 1:5 prednisolone:SLS coprecipitate and fastest disintegration time in the tablets of 1:1 prednisolone:SLS coprecipitate.

Among the three drug-single carrier coprecipitates prepared, the drug-dextrose coprecipitate is the most appropriate system for tabletting. The tablets prepared from drug-dextrose coprecipitate yielded very fast disintegration time and rapid dissolution rate.

The drug-PEG 4000 and the drug-SLS coprecipitates are unsuitable for tabletting since they gave tablets of slow disintegration times and the prepared tablets did not exhibit satisfied drug dissolution rates, except the system of 1:1 prednisolone:SLS coprecipitate.

For tabletting the use of high amount of PEG 4000 or SLS will cause retardation in the disintegration times of the tablets, and the improvement in dissolution achieved by solid dispersion may therefore be destroyed. Since PEG 4000 and SLS impart stickiness to the coprecipitates, the problem of tabletting will exist if too much PEG 4000 or SLS is used.

To improve the handling properties of the sticky and waxy materials flow aids and antiadherants are required (43). A disintegrant also is needed to counter the effect of binding (43).

Since indomethacin is available in market as capsule dosage form, therefore it is more appropriate to employ indomethacin-PEG 4000 or indomethacin-SLS coprecipitate as capsule dosage form.

In this way the dissolution retarding effect produced by compaction process is avoided.

B. Drug-Combined Carriers

Binding effect of PEG 4000 caused more retardation in disintegration times of the tablets containing 1:5 prednisolone:(dextrose-PEG 4000) or 1:1 indomethacin:(dextrose-PEG 4000) having higher ratio of PEG 4000:dextrose in the tablets.

For 1:1 indomethacin:(dextrose-PEG 4000) ratio, the higher disintegration times observed from the tablets of coprecipitate compared to the tablets of physical mixture having the same ratio of dextrose:PEG 4000 may be the result of less contact between the drug and PEG 4000 in the tablets of physical mixture. In the coprecipitate, indomethacin molecules were surrounded by molecules of PEG 4000 and dextrose therefore the binding effect of PEG 4000 on the tablets was more prominent in the tablets of coprecipitate compared to the tablets of physical mixture.

For 1:5 prednisolone:(dextrose-PEG 4000) and 1:1 indomethacin:(dextrose-PEG 4000) ratios, the improvement in dissolution rate of the tablets containing physical mixtures was due to the increase in wettability and solubility of drug particles imparted by dextrose and PEG 4000. The faster dissolution rates of the tablets containing coprecipitates compared to the tablets containing physical mixtures of the same ratio of dextrose:PEG 4000 was attributed to molecular or colloidal dispersion of drug in the combined carriers. The effect of disintegration time could be ignored since the comparable or

slower disintegration times were obtained from the tablets of coprecipitates.

Both glass dispersion of prednisolone or indomethacin in dextrose and interstitial solid solution of prednisolone or indomethacin in PEG 4000 was believed to be responsible for molecular or colloidal dispersion of the drug in the combined water-soluble carriers. The combined effects of glass dispersion and solid solution may produce more reduction in drug particle size or may result in higher amount of drug being dispersed at molecular or colloidal level than that obtained by dextrose glass dispersion or interstitial solid solution produced by PEG 4000 alone.

By using combined water-soluble system of dextrose-PEG 4000, small amount of PEG 4000 is needed. Its binding effect therefore is not high enough to retard tablet disintegration, in contrast this binding effect become helpful in tabletting. Besides PEG 4000 has been utilized as a lubricant in tablet formulation therefore no further lubricant is required. The presence of dextrose, a water soluble diluent, also improves the tablet disintegration time.

The 1:(3+2) prednisolone:(dextrose+PEG 4000) coprecipitate is the best system for incorporation into tablet dosage form followed by the 1:(2+3) prednisolone:(dextrose+PEG 4000) coprecipitate and the 1:(4+1) prednisolone:(dextrose+PEG 4000) coprecipitate respectively.

By using T_{80} as reference the coprecipitate of 1:(0.6+0.4) indomethacin:(dextrose+PEG 4000) gave the tablets of fastest

dissolution rate (T_{80} = 9.0 minutes) among the tablets of 1:1 indomethacin:(dextrose-PEG 4000), followed by the coprecipitate of 1:(0.4+0.6) indomethacin:(dextrose+PEG 4000) (T_{80} = 15.0 minutes).

Dextrose glass dispersion, solid solution, and increase in drug wettability imparted by SLS and dextrose were believed to be the reasons for drug dissolution rate enhancement in the tablets containing 1:5 prednisolone:(dextrose-SLS) and 1:1 indomethacin:(dextrose-SLS) coprecipitates.

The observed improvement in indomethacin or prednisolone dissolution of the tablets containing physical mixtures of drug and combined carriers, dextrose and SLS, was due to the wetting and solubilizing effects of dextrose and the surfactant SLS on the hydrophobic drugs since surfactants have been used to improve the dissolution rates of hydrophobic drugs by incorporation into solid dosage form (47).

The presence of SLS in higher amount caused more retardation in tablet disintegration. This disintegration retarding effect was responsible for the slow dissolution rates of the tablets containing 1:(1+4), 1:(2+3), and 1:(3+2) prednisolone:(dextrose+SLS) in the initial parts of their dissolution profiles.

Among the 1:5 prednisolone:(dextrose-SLS) coprecipitates, the system of 1:(1+4) and 1:(2+3) prednisolone:(dextrose+SLS) coprecipitates yielded tablets with slow disintegration times and hence slow initial dissolution rates, the tablets from these systems also gave comparable dissolution rates to the tablets containing

1:(1+4) and 1:(2+3) prednisolone:(dextrose+SLS) physical mixtures respectively. The system of 1:(4+1) prednisolone:(dextrose+SLS) coprecipitate although provided tablets of fast disintegration but not much enhancement in dissolution rate was observed compared to the prednisolone control tablets. The system of 1:(3+2) prednisolone :(dextrose+SLS) coprecipitate produced the tablets of fastest dissolution rate however these tablets exhibited slow disintegration resulting in slower dissolution rate in the first 10 minutes than the prednisolone control tablets.

Among the tablets containing 1:1 indomethacin:(dextrose-SLS) physical mixtures, the tablets of 1:(0.6+0.4) and 1:(0.8+0.2) indomethacin:(dextrose+SLS) gave faster disintegration times than the tablets of 1:(0.2+0.8) and 1:(0.4+0.6) indomethacin:(dextrose +SLS) which resulted in their faster dissolution rates. The initial slower dissolution rates of the tablets containing physical mixtures than the indomethacin control tablets was the result of their slower disintegration times.

The tablets of 1:(1+4) or 1:(2+3) prednisolone:(dextrose +SLS) coprecipitate did not exhibit faster dissolution rate compared to the tablets of 1:(1+4) or 1:(2+3) prednisolone:(dextrose +SLS) physical mixture. At these high ratios of SLS:dextrose maximum wetting effect was already obtained. Hence dissolution of prednisolone from coprecipitate was essentially the same as from physical mixture.

The tablets of 1:(3+2) or 1:(4+1) prednisolone:(dextrose +SLS) coprecipitate showed faster dissolution rate than the tablets of 1:(3+2) or 1:(4+1) prednisolone:(dextrose+SLS) physical mixture. At these low ratios of SLS:dextrose, the effect of SLS on improving wettability of prednisolone was not high enough to mask the effect of molecular or colloidal dispersion in the tablets of coprecipitate. As the result the tablets of 1:5 prednisolone:(dextrose-SLS) coprecipitate having low SLS:dextrose ratio yielded faster dissolution rate than the tablets of 1:5 prednisolone:(dextrose-SLS) physical mixture.

For the 1:1 indomethacin:(dextrose-SLS) ratio, the tablets of coprecipitate exhibited faster dissolution rate than the tablets of physical mixture of the same ratio of dextrose:SLS. This effect was due to molecular or colloidal dispersion of drug in the combined carriers since the effect of tablet disintegration could be omitted because all the tablets of coprecipitates, except the tablets of 1:(0.4+0.6) indomethacin:(dextrose+SLS) coprecipitate, yielded comparable disintegration times to the tablets of physical mixtures having the same ratio of dextrose:SLS.

For 1:1 indomethacin:(dextrose-SLS) coprecipitates, they yielded tablets which gave more indomethacin dissolution enhancement comparing to 1:1 indomethacin:single carrier (dextrose or PEG 4000 or SLS) coprecipitates. This observation may derive from the combined mechanisms of glass dispersion and solid solution which

may cause more reduction in drug particle size or may result in higher amount of drug being dispersed at molecular or colloidal level than that achieved from glass dispersion or solid solution alone.

All the indomethacin tablets prepared from the 1:1 indomethacin:(dextrose-SLS) coprecipitates meet the USP XXI & NF XVI dissolution requirement for indomethacin solid dosage form (2).

Usually SLS in small amount is used as lubricant in tablet formulation. Since SLS is used in small amount in preparing of 1:1 indomethacin:(dextrose-SLS) coprecipitate therefore the prepared coprecipitate is self lubricating and suitable for tabletting.

PEG 4000 is hydrophilic polymer with no hydrophobic moiety therefore is not surface active agent, while SLS is a surface active agent. The wetting and solubilizing effects on indomethacin particles should be higher in the tablets of 1:1 indomethacin:(dextrose-SLS) physical mixture than in the tablets of 1:1 indomethacin:(dextrose-PEG 4000) physical mixture having the equal amount of SLS to PEG 4000. Although the presence of SLS in indomethacin tablets caused slower tablet disintegration time compared to the indomethacin tablets having the equal amount of PEG 4000 presented, the T_{80} produced by the tablets of 1:(0.2+0.8), 1:(0.4+0.6), 1:(0.6+0.4), and 1:(0.8+0.2) indomethacin:(dextrose+SLS) physical mixtures are faster than the T_{80} produced by the tablets of 1:(0.2+0.8), 1:(0.4+0.6), 1:(0.6+0.4), and 1:(0.8+0.2) indomethacin:(dextrose

+PEG 4000) physical mixtures respectively. Therefore the wetting and solubilizing effects on indomethacin produced by SLS were higher than that produced by PEG 4000.

The more solubilizing and wetting effects of SLS was thought to make SLS be better carrier for coprecipitation of indomethacin than PEG 4000. This may be true since all four ratios of dextrose: SLS utilized in preparing of 1:1 indomethacin:(dextrose-SLS) coprecipitates yielded the tablets which meet the USP XXI & NF XVI indomethacin dissolution requirement for indomethacin solid dosage form (2) while only two ratios of dextrose:PEG 4000 employed in preparing of 1:1 indomethacin:(dextrose-PEG 4000) coprecipitates yielded the tablets which meet the requirement.

Table 22 and 23 represent dissolution parameters of prednisolone and indomethacin tablets prepared from some coprecipitates which are believed to be good systems for incorporation into direct compression tablets.

Conclusion

The results obtained from this investigation indicate that in most cases the coprecipitates of prednisolone or indomethacin with the combined water-soluble carriers of dextrose-PEG 4000 or dextrose-SLS are better systems for incorporation into tablet dosage form than the coprecipitates of prednisolone or indomethacin with the single water-soluble carrier of dextrose or PEG 4000 or SLS.

When the optimum ratios of dextrose:PEG 4000 or dextrose:SLS were selected, the tablets prepared from drug-combined carrier

Table 22. Dissolution Parameters of Prednisolone Tablets Prepared from Some Coprecipitates

TABLET CONTAINING COPRECIPITATE OF	T_{60}[1](MIN)	T_{90}[2](MIN)	C_{60}[3]
1:(3+2) Prednisolone:(dextrose+PEG 4000)	3.0	9.0	110.4 ± 0.44
1:(2+3) Prednisolone:(dextrose+PEG 4000)	5.0	10.5	110.5 ± 0.48
1:(4+1) Prednisolone:(dextrose+PEG 4000)	5.0	15.0	104.7 ± 0.49
1:1 Prednisolone:SLS	5.0	18.5	99.1 ± 1.61
1:(3+2) Prednisolone:(dextrose+SLS)	9.5	16.0	97.9 ± 2.73

[1] T_{60} = The time required for 60% prednisolone dissolution.

[2] T_{90} = The time required for 90% prednisolone dissolution.

[3] C_{60} = % Prednisolone dissolved obtained at the time of 60 minutes.

Table 23. Dissolution Parameters of Indomethacin Tablets Prepared from Some Coprecipitates

TABLETS CONTAINING COPRECIPITATE OF	T_{80}[1](MIN)	T_{90}[2](MIN)	C_{60}[3]
1:(0.6+0.4) Indomethacin:(dextrose+PEG 4000)	9.0	13.0	99.1 ± 0.06
1:(0.8+0.2) Indomethacin:(dextrose+SLS)	10.0	14.0	97.0 ± 0.48
1:(0.6+0.4) Indomethacin:(dextrose+SLS)	12.5	15.0	101.0 ± 0.08
1:(0.4+0.6) Indomethacin:(dextrose+SLS)	14.0	17.5	95.1 ± 0.26
1:(0.4+0.6) Indomethacin:(dextrose+PEG 4000)	15.0	21.5	97.2 ± 1.17
1:(0.2+0.8) Indomethacin:(dextrose+SLS)	17.5	20.0	100.7 ± 0.74

[1] T_{80} = The time required for 80% indomethacin dissolution.

[2] T_{90} = The time required for 90% indomethacin dissolution.

[3] C_{60} = % Indomethacin dissolved obtained at the time of 60 minutes.

coprecipitates exhibited more improvement in drug dissolution rate than the tablets prepared from drug-single carrier coprecipitates.

In most cases the tablets prepared from drug-carrier(s) physical mixtures yielded faster dissolution rates than the control tablets except in some cases where the disintegration times of the tablets of physical mixtures were much slower than the control tablets.

The use of dextrose-PEG 4000 and dextrose-SLS as combined water-soluble carriers for coprecipitation seems to offer unique opportunity for preparing coprecipitates which are suitable for incorporation into tablet dosage form. However, the optimum ratio of dextrose:PEG 4000 or dextrose:SLS must be chosen in order to get the tablets which exhibited fast disintegration and provided high dissolution rate enhancement.

The use of these two combined water-soluble systems can be applied to many other poorly water soluble drugs as well.