CHAPTER V

DISCUSSION

The principal goal of this chapter is to understand the nifedipine solid dispersion system and the related factors affecting its dissolution rate, for instance, type of carriers used, drug to carrier ratio and preparation methods. The physicochemical characteristic studies together with the literature review provide the useful information to explain the obtained results.

1. Nontreated pure nifedipine and treated pure nifedipine.

1.1 Dissolution behavior.

The dissolution profiles revealed that treated pure nifedipine by various methods were apparently not different from its physical mixture. All treated pure nifedipine dissolution profiles were lower than that of nontreated pure nifedipine. The reason was possibly the agglomerate of nifedipine particles in treated drug caused a lower specific surface area, hence, poorer dissolution profiles.

1.2 Physicochemical characteristics.

The melting endothermics of pure nontreated nifedipine show quite similar characteristics to those of treated nifedipine by physical mixing, melting, solvent, and kneading method at 174.4-178.0°C. This indicated that the experimental condition in the four methods had no effect to nifedipine thermal property and stability.

From X-ray diffraction, there was no difference between nontreated and treated nifedipine pattern and the major peaks at 7.9, 10.3 and 11.7° at 2θ were existed in each methods. The result from IR also revealed that the pattern peaks of IR were all the same as nifedipine itself. This suggested that any changes to X-ray diffraction peaks and IR pattern will cause by the studied factors not by any other influences.

2. Solid dispersion of nifedipine with various carriers.

Solid dispersion of nifedipine with PEGs, poloxamers and β-cyclodextrins were studied in terms of dispersion rate and physicochemical characteristics. In general, dissolution rates obtained from nifedipine solid dispersed in poloxamer showed favorable results followed by those obtained from nifedipine-PEGs and nifedipine-β-cyclodextrins respectively. A comprehensive discussion are made as followed.

2.1 Nifedipine-PEGs solid dispersion.

2.1.1 Dissolution study of nifedipine-PEGs solid dispersions.

The two way analysis of variance (ANOVA) showed statistically significant difference between method, ratio and the interaction between method and ratio for both PEG4000 and PEG6000. This means that ratio, method and combined ratio-method influenced the dissolution rates.

For PEG4000, the most favorable dissolution rate were found at the drug to carrier ratio of 1:10 in all methods. Melt method with drug-carrier ratio 1:10 and solvent method also with the ratio of 1:10 yielded the highest dissolution rates. However they were not significantly different in terms of LSR test.

The most favorable ratio, drug to carrier of 1:10, found in this study seemed to agree with Save and Vankitachalam (1992). For the nifedipine-PEG system, it was suspected that the drug-carrier ratio of 1:10 was a saturation point where PEG presented in a metastable form.

There was also a similar kind of report regarding the saturation level of carrier in nifedipine-PVP system. Nozawa, Mizumoto and Higashide (1986) reported that nifedipine crystals in the roll mixing with PVP 25% seemed to be converted to amorphous state easily.

PEG6000 exhibited similar dissolution results as those described in PEG4000.

2.1.2 Physicochemical characteristics of nifedipine-PEGs solid dispersions.

The photomicrograph of nifedipine-PEGs systems mainly showed that nifedipine particles physically deposited on the surface of the carriers. The observation of sides and corners found in both PEG4000 and PEG6000 suggested that PEGs may present in the crystalline state whereas nifedipine may not present in the crystalline state since the particles have already distorted from the pure drug. This phenomenon became clearer in the case of solid dispersions prepared by melting and solvent methods at higher ratios. The average particles size of nifedipine were found to be smaller than nontreated nifedipine.

For the nifedipine-PEG4000 systems, only at lower proportion of PEG4000 (at 1:1) that a broad endothermic peak which referred to nifedipine melting point could be observed at the temperature range 145°-162°C. These lowering melting point of nifedipine, from initially 175°C, depended on the preparation methods. Nifedipine solid dispersions showed lower melting endotherms than that of physical mixture. The lowest temperature of endothermic peak was found in the solid dispersion by solvent method.

It was found that only at 1:1 ratio of the physical mixture of PEG4000 that a small endothermic peak at 230°C could be detected. This peak might indicate the decomposition of nifedipine at very high temperature.

Since it was obvious that nifedipine melting could not be observed in solid dispersions including physical mixtures when the ratio of drug to PEG4000 other than 1:1. The explanation of these finding may be in terms of amorphization of nifedipine in crystalline state of PEG4000. (Figure74-77)

Similar DSC thermograms were obtained in the nifedipine-PEG6000 systems that PEG6000 melting endotherms could be found in all systems slightly lower than that of pure PEG6000. Broadened melting endotherms of nifedipine could be detected at all ratios of physical mixture, only 1:1 ratio in melting method, 1:1 and 1:3 ratios in solvent method and 1:1, 1:3 and 1:5 in DSC thermograms.

The IR spectra of nifedipine-PEGs solid dispersions, in general, did not show significant difference from their corresponding physical mixtures. Also, solubility showed the similar result between PEG4000 and 6000. However in

terms of wettability, PEG4000 had lower contact angle, therefore higher wettability.

X-ray diffraction patterns of nifedipine-PEG4000 at the ratio of 1:10 prepared by melting and solvent methods showed nearly disappeared of nifedipine peak whereas the peak corresponding to PEG4000 still remained as depicted in Figure 131-132. This also reconfirmed that nifedipine was transformed into amorphous form. Nifedipine could be dispersed homogeneously as an amorphous state within the crystalline PEGs.

PEGs systems were also reported in other publications. McGinity, Maincent and Steinfink (1984) reported an improvement of tolbutamide dissolution rate from solid dispersion with PEG. It was found that the main mechanism was the transformation of tolbutamide into amorphous state in crystalline PEG.

This was also similar to the report of Chiou and Niazi (1971) where urea (carrier) was present in a crystalline form, while the sulphathiazole (drug) showed no diffraction peak referred to sulphathiazole crystals which meant that transformation of drug to amorphous form.

As far as the ratio concern, the drug-carrier ratio below 1:10 exhibited slight nifedipine peaks and intense PEG peaks. The combined explanations of Save and Venkitachalam (1992) and Chiou and Niazi (1971) can be applied to explain this phenomenon. At the drug-carrier ratio below 1:10, nifedipine might partly change to an amorphous form remaining some crystals. X-ray diffraction of solid dispersion with the ratio lower than 1:10 therefore still showed some intensity of nifedipine peak.

Comparison between nifedipine-PEG4000 and nifedipine-PEG6000, it was found that the dissolution rate constants from nifedipine-PEG6000 were just slightly higher than that of nifeipine-PEG4000. Ford (1986) reviewed the mechanisms for the system where the dissolution rates increase with increasing molecular weight of PEG. The positive factors that may enhance dissolution rate when the molecular weight is increased are higher viscosity hence reducing drug crystallization, increase tendency the incorporation of drug as solid dispersion and readily flake during dissolution.

2.2 Nifedipine-poloxamers solid dispersion

2.2.1 Dissolution behavior of nifedipine- poloxamers solid dispersions.

The two way analysis of variance indicated statistically significant difference between method, ratio and the method-ratio interaction for all of poloxamer system. The most favorable dissolution rate was poloxamer188 by melting method at the ratio of drug to carrier 1:3 followed by 1:10 ratio of poloxamer407 by melting method and at 1:10 ratio of poloxamer288 by melting method.

In poloxamer188 system, the ranked order from the highest dissolution rate was melting 1:3, melting 1:5, kneading 1:10 and solvent 1:10, for poloxamer407 the ranking was melt 1:10, knead 1:10, solvent 1:10, melting 1:5 and for poloxamer288 the ranking was melting 1:10, melt 1:5, solvent 1:10 and kneading 1:10 respectively.

2.2.2 Physicochemical characteristics of nifedipine-poloxamers solid dispersions.

The observation of photomicrograph showed very interesting features in the systems of poloxamers. Pure carriers showed very smooth surface liked melted wax. Fewer drug particles were found in this system compared with the other systems. Instead, it was found that the drug particles embedded into the surface of the carriers, not just physically deposited on it. SEM results were found to be closely related to dissolution rate. The more implantation of drug to the carrier, the better dissolution was found. Nifedipine-poloxamer188 at the ratio of 1:3 showed highest drug implantation followed closely by poloxamer288 at the ratio of 1:10.

DSC thermogram showed similar patterns to those of PEGs. A sharp endothermic peak of poloxamer melting was shown in every systems, interestingly at the temperature lower than that of its pure corresponding poloxamers. It could be noticed that the lowering of melting points was different among the four preparation methods.

As the proportion of nifedipine decreased, at ratio 1:3, 1:5, 1:10, nifedipine melting could not be observed. This might be explained that the dispersion of nifedipine was greater with higher proportion of poloxamers, nifedipine appeared as very small particles of amorphous form dispersed in crystalline poloxamers. Certainly, this could be confirmed with the X-ray diffraction patterns (Figure 83,87 and 91)

From the X-ray diffraction of poloxamer systems, similarly to the dispersion with PEGs system, the crystallinity of nifedipine gradually decreased with the proportion of carriers increased and the peaks of both

poloxamers and PEGs still existed in both systems in most methods. The endothermic peak of nifedipine from the DSC was disappeared in the solid dispersion. The SEM depicted the smooth surface and wax like particles. From these physicochemical properties shown that the solid dispersion with poloxamer, nifedipine also possibly presented in an amorphous dispersing in crystalline carrier.

From the wettability and solubility studies, it was found that all solid dispersion with poloxamer was not easily wetted compared with PEGs and β-cyclodextrins. However all poloxamers showed higher solubility than that of PEGs and β-cyclodextrins. One can predict that dissolution rate of solid dispersion with poloxamers, in general, would yield a higher dissolution rate than the solid dispersion with PEGs due to solubilizing effect.

Among poloxamers themselves, poloxamer188 gave the highest dissolution rate constant, of course among all carriers studied. The ranked dissolution rates from the highest is as poloxamer188 > poloxamer288 > Poloxamer407. Table below shows some key properties that may play important role in dissolution mechanisms (extracted from (a) Nikitakis, 1988 (b) Miyazaki et al., 1986 (c) BASF, 1987 and (d) results from this experiment).

Table 20 Physicochemical characteristics of poloxamers.

Poloxamers	188	288	407	Sources
Melting point (°C)	54.6	60.5	57.5	a, b
Molecular weight	8350	13,500	11,500	a, b
POE: POP ratio	80 : 20	80 : 20	70 : 30	a, b
Hydrophobe weight	1750	2750	3850	a, b
HLB	> 24	>24	18-23	c
Viscosity-Brookfield (cps)	1,000	2,700	3,100	c
Surface tension (dynes/cm)	50	43	41	c
Contact angle (θ)	30	40	50	d
Solubilizing effect	9.5-19.3	11.25-29.31	32.5-214.4	d

From the results of dissolution study, it could be shown that poloxamer188 was superior, that showed highest dissolution rate constant and remarkably high $T_{80\%}$, followed by poloxamer407 and poloxamer288, respectively. It should be noted here that poloxamer407 showed the highest solubilizing effect but yet not gave the highest dissolution rate. The dissolution rate constant obtained from solid dispersion with poloxamer407 was lower than that of poloxamer188. This may be due to the viscosity. It is ranked from the highest to the lowest as poloxamer407 > poloxamer288 > Poloxamer188. The viscosity from poloxamer407 was about 3 times higher than that of poloxamer188 but close to polxamer288. This may cause the thicker diffusional layer for the drug to transport to water.

Braun and Parrott (1972) and Morita and Hirota (1982) showed that viscosity, at certain level, might reduce the dissolution rate of the drug. This

may be the key reason for explaining poloxamer systems. Poloxamer407 has the viscosity three time higher than that of poloxamer188. Even though the solubilizing effect of poloxamer407 was high, the viscosity seemed to be prevail in the systems studied. Viscosity may play an important role in inhibiting drug crystallization, in other words polymorphic transformation. However in the system of poloxamer407, the viscosity may be excessive for inhibiting nifedipine crystallization. Instead, the thicker diffusional layer was built.

2.3 Nifedipine-cyclodextrin solid dispersion.

2.3.1 Dissolution behavior of nifedipine-cyclodextrins solid dispersion.

The results from two way ANOVA revealed that β-cyclodextrin and 2-hydroxypropyl-β-cyclodextrin had significant difference between method of preparation and between ratio in preparation but there was no statistical difference between method and ratio interaction at 95% confidence interval.

It was shown that the dissolution rate constant of kneading method of β-cyclodextrin at 1:5 ratio gave the highest dissolution value among the dispersion of β-cyclodextrin which can be prepared and at 1:10 ratio of kneading method gave the maximum dissolution rate constant of 2-hydroxypropyl-β-cyclodextrin.

2.3.2 Physicochemical characteristics of nifedipine-cyclodextrins solid dispersions.

In the β-cyclodextrin systems, similar DSC thermograms were obtained in the physical mixtures and kneaded products. Two endotherms that referred to nifedipine melting at 175 °C and water dehydration of β-cyclodextrin at about 130-160 °C exhibited in all ratios. The latter endothermic peak was also found in Guyot et al. (1995) in the range of 120-150 °C whereas Kedzierewicz, Hoffman an Maincent (1990) reported the endothermic peak of β-cyclodextrin stretching between 50-125 °C and dehydration of tolbutamide-β-cyclodextrin complex between 50-163 °C. From the DSC thermogram conducted by Miazzi et al. (1988) also showed the dehydration of β-cyclodextrin began at about 55-160 °C.

The endothermic peaks of nifedipine became smaller and nearly fused to those of β-cyclodextrin at the ratio of 1:5 and 1:10 of kneaded mixtures. This might be due to nifedipine particles were dispersed more closely by β-cyclodextrin particles at higher proportion of β-cyclodextrin.

For the system of 2-hydroxypropyl-β-cyclodextrin, the solid dispersions prepared by solvent method exhibited different thermograms from the physical mixtures and kneaded mixtures. At the higher proportion of 2-hydroxypropyl-β-cyclodextrin, at the ratio of 1:3, 1:5. 1:10, nifedipine melting endotherm could not be detected. These were in agreement with their X-ray patterns (Figure 97) that nifedipine dispersed in amorphous form in the carrier.

Hirayama, Wang and Uekama (1994) explained the DSC thermogram of nifedipine in details. The glassy state of nifedipine was prepared in an absence and presence of 2-hydroxypropyl-β-cyclodextrin. The glassy nifedipine was

reported at an endothermic peak at 48 °C, an exothermic peak at 105 °C was the crystallization to a metastable form of nifedipine (form B), an exothermic peak at 125 °C was the polymorphic transititon of form B to form A and an endothermic peak at 171 °C for the melting of form A. It was also found that in presence of 2-hydroxypropyl-β-cyclodextrin, the exothermic at 125 °C for the form B to A transition disappeared and a new endothermic peak appeared at 163 °C.

In this study, only the endothermic peak responding to the melting point of form A was found. The appearance of exothermic peak at 125 °C and endothermic peak at 163 °C were not observed.

For the nifedipine-β-cyclodextrin system, X-ray diffraction revealed that dispersion of β-cyclodextrin still had crystallinity peak of the carrier itself and major peaks of nifedipine in kneading method and physical mixture. The results of DSC were in line with the X-ray diffraction pattern that still found the endothermic peaks of nifedipine at 167-174°C in each ratio of kneaded and physical mixed products. These explained why the solid dispersion with β-cyclodextrin had lower dissolution rate than that of poloxamers and PEGs. Even though β-cyclodextrin gave the best wettability value (the contact angle was 0° at 1:10 ratio), the solubility effect of β-cyclodextrin was low in its solubility range.

In conclusion, β-cyclodextrin would have helped wetting of nifedipine in the first time of dissolution as it showed higher dissolution rate than the pure drug. However β-cyclodextrin did not form complex which seemed to be agree with the experiment of Acarturk, Kislal and Cebbi (1992) who explained that the enhanced dissolution rate of nifedipine -β-cyclodextrin may be due to the

increase in solubility from β-cyclodextrin and its complex had not been completely formed in the solid state.

For 2-hydroxypropyl-β-cyclodextrin dispersion system, kneading method at the ratio of 1:10 gave the maximum dissolution rate constant among its group followed by solvent 1:10 which showed no statistical difference from kneading method. The DSC data exhibited the existence of sharp endothermic at the peak of nifedipine at 171-174°C which supported the evidence of the absence of complex formation in this system. If the complex formation had occurred, the endothermic peak of nifedipine would have been broadened as described by Nagarsenkar and Shenia (1996). Moreover the result of IR spectra revealed that scanned peaks of the dispersed products in each method were not different with those spectra obtained from physical mixtures.

Similarly to the study of Veiga and Espanol (1995) who found that oxodipine, a very similar drug to nifedipine, did not truley form inclusion complex with 2-hydroxypropyl-β-cyclodextrin. Instead, it was suspected that oxodipine particles was coated by 2-hydroxypropyl-β-cyclodextrin and help improve the dissolution rate.

Becirevic-Lacan et al. (1996) studied the formation of nifedipine complexes with β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin and heptakis (2,6-di-O-methyl)-β-cyclodextrin prepared by freeze drying, spray drying and physical mixing methods. It was found that drug in the freeze dried product was probably totally complexed while the spray dried product could contain a mixture of complexed and uncomplexed drug and physical mixed product, in contrast, did not form complex. Extrapolation made from their study to this study, it could be assumed that solvent method and kneading methods would hardly stimulate complex formation when compared to spray drying method. In

this sense it is therefore sensible to find negligible complex formation occurred in solid dispersion prepared by solvent method and kneading methods in this experiment.

Moyano et al. (1997) studied solid complex between gliazide and β-cyclodextrin prepared by kneading, coprecipatation, neutralization, co-grinding and spray drying methods. Only neutralization and spray drying methods were found complex formation. The conclusion was then made as the extent of the enhancement of the dissolution rate, whether conclusion complex was formed, was somewhat dependent on the preparation methods. Palmieri et al. (1997) also reported similar result for the drug of methoxybutropate which form the soluble complex when prepared by spray drying method but not by kneading and solvent methods.

Not only the method used, drug to carrier ratio was also found to be another factor involving this mechanism. Palmieri, Wehrle and Martelli (1998) reported that the complexation percentages are acceptable only for the spray dried powders with 1:4 drug-β-cyclodextrin molar ratio specifically for lonidamine.

The wettability data showed that the contact angle of 2-hydroxypropyl-β-cyclodextrin were in the range of 25-40° and the contact angle decreased with an increase in carrier weight ratio. 2-Hydroxypropyl-β-cyclodextrin showed similar solubilizing effect to that of poloxamer188 in the range of 0-4% of carrier weight ratio. 2-Hydroxypropyl-β-cyclodextrin and nifedipine in kneaded product were vigorously contacted between molecules because of the compression force possibly causing a weak interaction.

Comparing between the system in PEGs and poloxamers with cyclodextrins, it was found that the system of cyclodextrins had lower dissolution rate than those systems. The main reason was possibly due to lesser amorphous transformation.