CHAPTER IV

DISCUSSION

HCTZ was poorly wetted due to its hydrophobicity. It aggregated and floated on the water surface so its dissolution was slow. Since chitin and its derivatives enhanced the dissolution of several poorly soluble drugs (Sawaganagi, 1983). In this study, efforts to improve HCTZ dissolution were investigated using CT, CS, CSU and LMCS through several dispersion methods compared with two popular carriers, PVP and PEG. The carriers used in the experiment were divided into two groups, water soluble and water insoluble. LMCS, PVP and PEG were water soluble, while CT, CS and CSU were water insoluble. All of them were within controlled particle size range of 60/100 mesh. Processing methods consisted of physical method, kneading method, solvent method of solid dispersion, solvent deposition method and ball milling method of solid surface dispersion. These methods were easy and simple and could be used in production scale. The results illustrated that most HCTZ dispersion systems exhibited satisfactorily faster dissolution than its corresponding physical mixtures and pure drug, either treated or untreated. Different dispersion methods with the same carrier showed different dissolution patterns. For most dispersions, the more amount of carrier the more dissolution of drug. The summarization of $t_{80\%}$, the time that was taken to dissolve 80% of HCTZ, is shown in Table 5.

HCTZ

The dissolution of HCTZ and treated HCTZ revealed that most treated HCTZ showed no increment of HCTZ dissolved except at the early stage of HCTZ BM. In contrast, the dissolution of HCTZ SM was significantly decreased.

The morphology and size of HCTZ PM were the same as pure HCTZ. Both had wide particle size range. Size reduction and surface roughness appeared on HCTZ KM, although the melting endothermic peak at 272° C was the same as HCTZ which implied that kneading did not change its crystallinity. However, like conventional granulation, kneading tended to adhere fine particles(<50 μm) together and onto large particles. Therefore, the total surface area of HCTZ KM might be the same as pure drug.

Table 6 The Time 80% of HCTZ from powder dissolution.

THE TIME 80% (MIN :SEC)					
Carrier	Ratio (drug:carrier)	METHOD			
		PM	KM	SM/SMD	BM
-	1 : 0	24 : 00	22 : 50	38 : 11	29 : 55
CT	1 : 1	15: 21	6 : 17	8 : 16	1 : 53
	1 : 2	14 : 58	6 : 42	5 : 54	1 : 34
	1 : 3	13 : 23	5 : 31	6 : 53	1 : 34
CS	1 : 1	16 : 08	4 : 43	15 : 45	2 : 22
	1 : 2	15 : 09	4 : 43	14 : 34	1 : 34
	1 : 3	13 : 35	5 : 54	9 : 27	1 : 34
CSU	1 : 1	26 : 23	8 : 16	12 : 12	21 : 16
	1 : 2	20 : 04	7 : 05	7 : 29	11 : 49
	1 : 3	17 : 43	7 : 29	7 : 29	14 : 10
LMCS	1 : 1	10 : 52	1 : 47	3:30/10:09	1:53/2:00*
	1 : 2	9 : 30	1 : 54	1:51/19:50	3:56/3:21*
	1 : 3	10 : 15	1 : 56	1:51/20:00	3:34/3:11*
PVP	1 : 1	44 : 05	7 : 05	14 : 58	5 : 07
	1 : 2	33 : 28	6 : 42	11 : 49	5 : 07
	1 : 3	37 : 24	5 : 31	7 : 07	4 : 32
PEG	1 : 1	20 : 04	14 : 10	6 : 17	-
	1 : 2	17 : 43	10 : 14	5 : 07	-
	1 : 3	12 : 12	8 : 40	2 : 22	-

* Swinging mill / Vibrating mill

Different polymorph with some amorphous form of HCTZ were evidently obtained from solvent deposition method supported by cuboid morphology, lower melting point and different X-ray diffraction angles with higher baseline. Due to the decreasing melting endotherm, higher dissolution was expected. However the decreased dissolution was probably caused by strong attraction force within compacted crystals. Similar melting endotherm and X-ray diffraction spectra of HCTZ BM to HCTZ SM refered to the same polymorph. Thus, their dissolution should be the same. However, ball milling reduced the size of HCTZ to less than 10 μm though some were aggregated. This submicron level of HCTZ BM was markedly smaller than the size of other HCTZ. Therefore, faster dissolution was exhibited. However, after 10 minutes, its dissolution was gradually closer to that of HCTZ SM.

The Effect of Carriers and Drug : Carrier Ratios

A) HCTZ - CT Dispersion systems

Dispersion of CT in HCTZ clearly enhanced the drug dissolution especially in ball milling method. The order of dissolution was as followed: CT BM>> CT KM>CT SMD>CT PM > pure HCTZ.

Physical mixing of drug and CT did not alter their own characteristic. Both ingredients were interparticulately mixed. The increased dissolution of HCTZ from physical mixtures was simply attributable to the disintegration effect of CT. CT could be swollen in water to produce hydration (Muzzarelli, 1977) . Particles were thus deaggregated and wetted.

In kneading method, the drug and carrier were intraparticulately mixed. The disintegration effect of CT was more prominent than in physical mixing method. Particles were disintegrated into fine particles, deaggragated and wetted. Therefore, their dissolution was greater. Since CT could not dissolved in ethanol, the prepared dispersion was solvent deposited. The dissolved drug, after evaporation of the solvent, would finely deposit onto the surface of CT. The obtained drug had the same crystallinity as HCTZ SM but was much smaller and deaggregated. This led to better dissolution than both HCTZ SM and CT PM. Increasing the amount of carrier increased the surface area for drug deposition which leaded to greater surface area of drug particle and better drug dissolution.

In all cases, ball milling with CT produced better dissolution than other drug-CT mixtures. This showed the same results with Sawayanagi et al.

(1983) who reported that dissolutions of prednisolone and phenytoin from ground mixtures with chitin were significantly enhanced. In the experiment, as the balls impacted on the mixture, curly sheet was changed to small flatly sheet with rougher surface of the finely deposited drug. This strong grinding force greatly disturbed the drug molecule than other dispersion techniques. Therefore, more crystal size reduction and more amorphous drug, as disclosed by lesser intensity peaks with higher baseline in X-ray diffraction pattern, were obtained. Although no polymorphic alteration and chemical complexation from X-ray diffraction pattern and IR spectra, the melting endotherm was markedly lowered and broader around 247 °C due to amorphism of drug. This lowering of HCTZ melting point resulted in the dissolution enhancement. Including the disintegration effect of CT, CT BM exhibited superiority of dissolution over other CT systems.

B) HCTZ-CS Dispersion systems

Like CT dispersion systems, the dissolution of HCTZ in CS dispersion was clearly enhanced especially from CS BM and was in the same order : CS BM >> CS KM > CS SMD > CS PM > pure HCTZ.

CS, the deacetylation product from CT, was more widely used due to its solubility in acid solution. Thus the improvement of dissolution, including drug crystal changed, was due to both effects of being as disintegrants with rapid dissolution in acid medium. From this reason CS dispersions should exhibit higher dissolution than CT dispersions. However, slight difference was observed.

In physical mixture the drug and CS were only interparticulately mixed while intraparticulate mixing was observed in kneading mixture. Thus the effect of increased dissolution with CS was more obvious in kneading mixture than in physical mixture. By solvent deposition technique, CS SMD also showed the same polymorph as HCTZ SM and CT SMD. The finer drug obtained was deposited onto the surface of CS. However, its dissolution was not higher than that of CT SMD indicating that multilayered deposition of drug onto the surface of CS might be present. Thus, the dissolution was not maximized. For CS BM the dissolution obtained was the highest compared to other HCTZ-CS dispersion. This was explained by the aforementioned milling technique. Disappointedly the dissolution of HCTZ from CS BM was slightly lower than that from CT BM, due to the larger average particle size range of CS BM in SEM. This was probably caused by the more rigid properties of chitin structure than chitosan which may result in a smaller size dispersion of drug and chitin.

C) HCTZ-CSU Dispersion Systems.

As an attempt on utilizing the local source, CSU was used to compare with CS. The result of dissolution between both types of dispersion showed some difference in each dispersion technique, especially in ball milling. Comparision of $t_{80\%}$ between CS and CSU dispersions was shown in Figure 58. The order of increased dissolution was : CSU KM > CSU SMD > CSU BM > CSU PM > pure HCTZ.

Different sources or processing of any material may lead to different characteristic of the product. The IR spectra in Figure 56 revealed that CSU had lesser degree of deacetylation and relatively higher molecular weight than CS. This spectrometry was a rapid method and conceded to observe the residual CONH groups in chitosan product (Miya et al., 1980). The higher the intensity of 1650 cm^{-1} band the higher the amount of carbonyl groups and the lower the deacetylation degree. The lower degree of deacetylation was normally caused by the shorter processing time of processing. Therefore, the hydrolysis of polymer chain was concurrently less, hence higher molecular weight of polymer was obtained.

Dispersions of HCTZ and CSU increased the dissolution by the same mechanism as those of CS. Some former dispersions exhibited better dissolution such as CSU SMD (1:2, 1:3) exhibited slightly higher dissolution than CS SMD (1:2, 1:3). However, most CSU dispersions showed slower and/or lesser dissolution than CS dispersions. This was due to the higher molecular weight of CSU resulting in higher medium viscosity, as the solution viscosity was basically a measure of the size or extension in space of polymer molecules (Flory, 1953). Thus diffusion of dissolved drug was slower. Higher viscous medium was obviously observed from the CSU than from CS during the dissolution test. This result was prominent in CSU BM which yielded poor performance of dissolution. After gel was formed when the mixture powder exposed to medium, and more time was taken to completely dissolve compared with CS BM which rapidly dissolved.

D) HCTZ-LMCS Dispersion Systems

Due to the limited solubility of both chitin and chitosan, LMCS the hydrolysis product which is extremely soluble in water has received considerable attention to survey the possible utility for improve the drug dissolution. Most dispersions of HCTZ with LMCS remarkably enhanced the dissolution. The degree of enhancement achieved was in the order : LMCS KM > LMCS SM > LMCS BM (SW, VB)> LMCS PM > LMCS SMD > pure HCTZ.

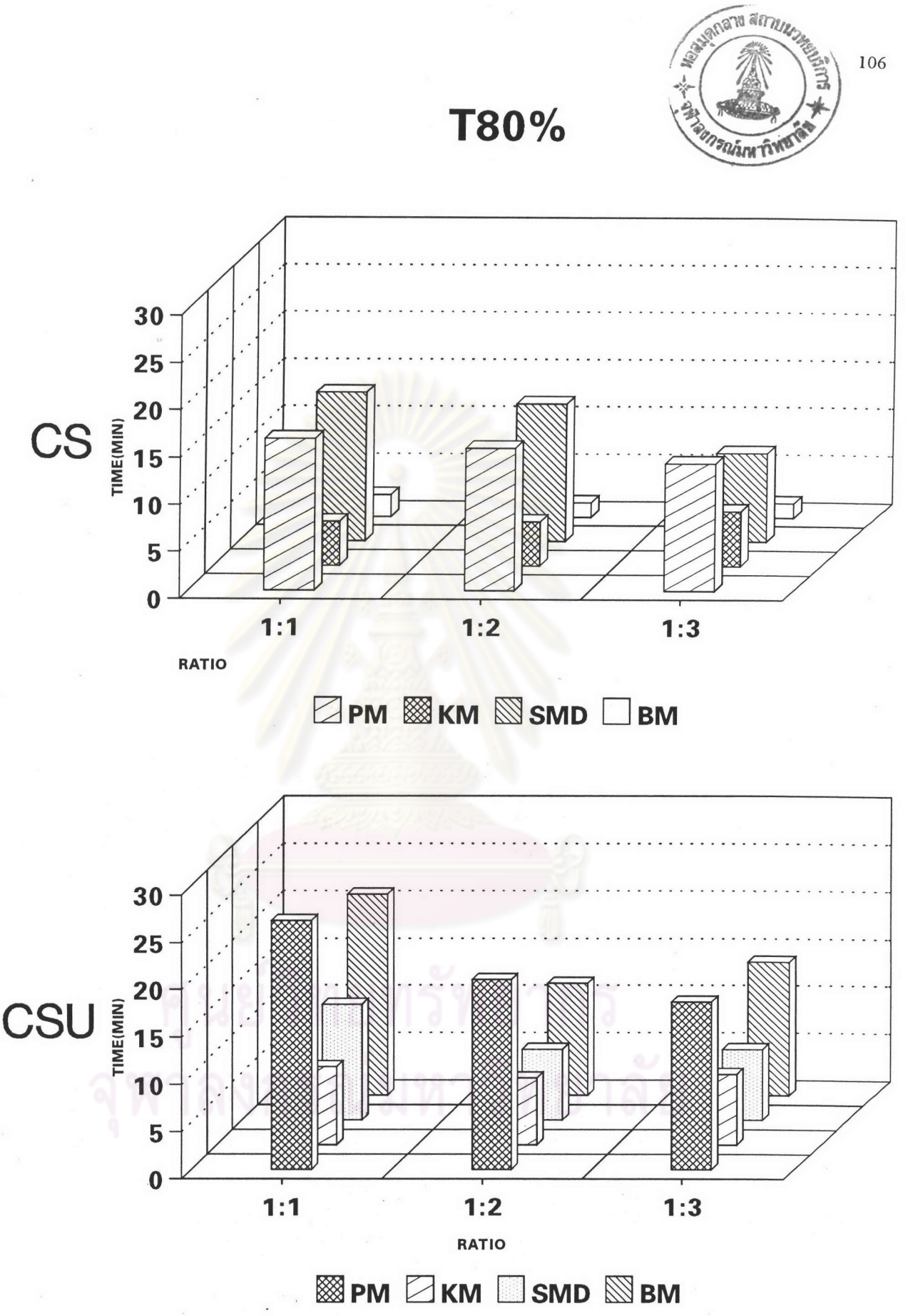

Figure 58 Comparison of $T_{80\%}$ between CS and CSU

Physical mixture of LMCS improved the dissolution of HCTZ less than other LMCS dispersions except LMCS SMD. This was due to the drug did not alter its solid characteristics. With only the hydrophilicity properties of LMCS, wettability of the drug was improved with lesser degree of agglomeration.

The dissolution obtained was the best in kneading mixture, LMCS KM was superior over other techniques and other carriers. Although essentially no interaction of drug with LMCS was observed from IR spectra, changes of drug crystals in the kneaded mixtures were apparent. The crystallinity of LMCS KM was changes similar to the pattern of HCTZ BM, but with more amorphism due to the decrease of crystallinity and/or microcrystal size, microcrystal shape. However, the rapid dissolution obvserved may not be fully explained by the crystal changes, as LMCS is very soluble in water, they may improve the wettability of drug particles by water through dispersion.This was in agreement with Shiraishi et al.(1990) who reported that the enhanced dissolution rate of kneaded mixtures of LMCS with any types of drugs was due to improvement of wettability and to changes of the crystallinity, microcrystal size and shape. In addition, further investigation should be needed for completly supporting the explanation due to DTA thermograms was changes to the same melting endotherm as LMCS SMD which may not be the reason on improvement dissolution.

For solvent technique, LMCS SM was superior to LMCS SMD. The dissolution of LMCS SM was increased and close to LMCS KM. Its crystal size was decreased and its shape was changed. Its showed small amount of amorphous form and/or change to new crystal form as indicated in different X-ray spectra from HCTZ BM. In LMCS SMD, the drug still remained the same crystallinity as other SMD systems. The dissolution drug was deposited onto the surface of carrier. Due to the riddle shape of LMCS, the increment of carrier ratio may caused more agglomeration thus decreased the total surface area for drug deposition.

For milling mixture, both SW and VB showed the same increased of dissolution. The obtained drug in both systems was the reduction in crystal size/shape and its crystallinity as same as other milling mixtures. Including the hydrophilicity of LMCS lead to an improve of the dissolution. Unlike CT and CS, milling with LMCS was not the best system and its dissolution also lesser than that of CT/CS BM. This may explained by the different of their particle shape as seen in the SEM. LMCS had riddle shape which led to more agglomeration during milling than the two dimension sheet shape of CT/CS. This agglomeration of LMCS together with the disintegration properties of

CT/CS caused the slower dissolution of LMCS BM than CT/CS BM. However, it is to mention that comparison between CT/CS BM and LMCS BM was not applicable due to the difference of ball mill type.

E) HCTZ-PVP Dispersion Systems

Since PVP of various molecular weights are commercially available, numerous publications reveiwed on the effect of molecular weight upon using. Generally, the dissolution of drug decreased as the molecular weight of carrier increased (doherty, 1987). In this study, PVP K30 was selected. The degree of enhancement achieved was as followes: PVP BM > PVP KM > PVP SM > pure drug > PVP PM.

In physical mixture, this carrier did not improve the dissolution. As both drug and PVP did not change its own characteristic in simple mixing. Therefore the properties of carrier in increasing medium viscosity would retard the dissolution (Geneidi, 1980). After kneading, the mixture showed different structure. New crystalline form looked like HCTZ BM but having some amorphism was obtained, thus increased the dissolution than physical mixture and pure drug.

For solvent method, homogeneous glassy mixture was obtained after evaporation of the appropriated solvent. The drug was molecularly dispersed in the carrier and dissolved faster than its own crystalline form. But the increment of dissolution was not higher as expected eventhough complete amorphism was obtained. However, the increase carrier ratio was markedly increase dissolution especially in 1:3 ratio. Thus the more amount of carrier should be used to improve dissolution satisfactory.

The highest dissolution from mixture of drug and PVP was obtained by ball milling method. Very fine dispersion with small amount of aggregates was obtained, the crystallinity of reduced to some amorphous characteristics, like other ball milling mixtures. However, this highest dissolution was still lesser than most of ball milling with chitin and its derivatives.

F) HCTZ- PEG dispersion systems

Since there are available molecular weight fraction of PEG, in this study, PEG 4000 was selected due to the suitability of molecular weight on improving dissolution.The dissolution of HCTZ was increased in all PEG

dispersion. The order of increase was as follows: PEG SM > PEG KM > PEG PM > pure drug.

In physical mixture the dispersions was only the combination of drug and carrier. Thus the enhancement in dissolution can be attributed to the increased wettability of the drug. The similar results have been reported in several systems (Craig, 1990). This improvement of wettability was more obvious in kneading mixture, as the drug was intraparticularly mixed with the carrier. The highest dissolution was obtained from solvent dispersion. This was due to after coprecipitated the significant amounts of drug, with proper of phase transition, could be entrapped in the helical interstitial space. Among those solvent dispersion, PEG SM markedly increased the dissolution close to LMCS SM.

The Effect of Dispersion Techniques

A) PM Technique

The dissolution of HCTZ from the physical mixtures were orderly enhanced : LMCS PM > CT PM > CS PM >PEG PM> CSU PM > PVP PM.

By this technique, the presence of carrier caused less agglomeration and/or improvement of wettability of the drug in carrier dispersion, resulted in better dissolution than those of control drug. However the amorphization or the reduction in particle size on the dispersion of drug in a micronized state was not obtained, thus the improvement of dissolution was less than other techniques.

The effect of carrier types on the dissolution was demonstrated. Hydrophilic carrier showed more improvement of dissolution than hydrophobic carrier, due to it owns superior wettability. LMCS was the best carrier when compared with PVP or PEG, which was also hydrohilic carriers, the latter showed less increment of dissolution. This results may due to their increment of medium viscosity as aforementioned. However hydrophobic carrier can improved dissolution by disintegrant effect.

B) KM Technique

The dissolution of HCTZ from the kneaded mixtures was significantly enhanced, especially LMCS KM, in the order of LMCS >> CS >CT>PVP>CSU>PEG>control drug (HCTZ, HCTZ KM). This method produced better dissolution than physical mixtures. This could be state that

kneading method help improvement of dissolution characteristics. Similar results were previously reported by many researchers (Shiraishi et al., 1990 ; Kimura et al., 1990; Imai et al., 1991).

In this experiment, kneading method was mainly to improve wettablity and change the solid stage the drug. The crystal form of HCTZ in any kneaded mixtures was the same as HCTZ BM but small amount of amorphous form was observed. This led to greater dissolution than physical mixtures.

Among the carriers, chitin and its derivatives exhibited higher dissolution than the comparative carriers PVP and PEG. The best carrier was LMCS which yield superior dissolution over other dispersions. However, CS KM may caused retardation of drug dissolved from tablet formulation if the unsuitable concentration was used. Sawayanagi et al. (1982) used chitosan as a vehicle for preparing direct compression matrix of propanolol hydrochloride tablets and zero-order controlled release of the drug was obtained.

C) SM Technique

The dissolution of HCTZ was increased through both systems of SM and SMD techniques, especially LMCS SM, and was in the order of LMCS SM > PEG SM > CT SMD > CSU SMD > PVP SM > CS SMD > LMCS SMD > control drug (HCTZ, HCTZ SM).

Both SM and SMD were used due to suitability of each carrier. Water soluble polymers - LMCS, PVP,and PEG had been selected for SM technique. While CT, CS and CSU which exhibited poor solubility in common solvents were for SMD technique. As the different techniques it should not be compare together. However, both techniques had been widely used to increase dissolution of many drug.

Generally in SM, drug particle size was reduced and dispersed molecularly in matrix of soluble inert carrier. While in SMD, the drug particle was deposited form the solvent onto the surface of inert carrier to obtain a high surface area by reduction of particle size (Monkhouse and Lach, 1972). From the experiment, SM technique produced better dissolution than SMD technique because the drug in SM become partially or completely amorphous while crystallinity of HCTZ still appeared in SMD. This was in agreement with Allen and Kwan (1969), that the degree of crystallinity in solid dispersion could markly influence the dissolution rate of a drug. In addition, the carrier in SMD may not possess extensive surface area thus the dissolution was not maximized.

For SM, dispersion with LMCS exhibited superior dissolution over its SMD dispersions and the comparative dispersion of PVP SM and PEG SM. However, PEG SM increased dissolution closed to LMCS SM, especially 1:3 PEG SM. This was predicted that the drug could be entrapped in the helical interstitial space of PEG structure resulting in molecular or colloidal dispersion of the drug after coprecipitate (Craig, 1990). While in PVP SM, although the completely amorphous state of HCTZ was obtained, the dissolution was still lesser. The possible explanation was the reduction of surface area when exposed to medium as observed during the dissolution test that PVP SM powder sank into the bottom and fused together thus hindered dissolution. In addition, the DTA thermogram of PVP SM had new complex at higher of melting endothermic peak (189° C) than PEG SM (about 53° C) and LMCS SM (about 87° C) indicating the lesser increment of dissolution than PEG SM and LMCS SM.

For SMD, most dispersion increased slower dissolution than those of SM dispersion except PVP SM. Chitin and its derivative in SMD dispersion showed better dissolution than those of control drug. When compared among these carriers, it was found that CT / CS / CSU SMD gave fast dissolution than LMCS SMD. This was inagreement with Chowdary and Madhusdhan (1990) that water insoluble carrier gave fast dissolution when compared to water soluble carrier which themselve dissolved leaving aggregated of the drug.

D) BM Technique

HCTZ in dispersed systems prepared by milling technique exhibited tremendous increment in dissolution. Most carriers caused significant improvement of dissolution compared with other techniques.

Generally, milling are used to produce fine particulate having increased surface area available for dissolution. Moreover, it has been previously report that milling not only reduced the particle size but also cause the changes in the molecular behaviors such as phase transition of polymorphs, crystallinity, and chemical reaction rate in solid phase (Nakai, 1986). Therefore the achieved dissolution was superior far from another simple mechanical techniques except for LMCS KM.

In this experiment, during milling the crystal structure of the drug molecule was disturbed, and changed to new crystal form or decreased crystal size/shape, and/or some amorphous state appeared without any chemical complexation. Beside crystal change, the increased dissolution was also depended on the carrier properties. As can be seen from HCTZ BM, the drug

tended to agglomerate therefore the applied force had less effect on the change of crystal structure of drug molecule. This indicated that the carrier had great effect on the drug crystal change. Milling caused depositing and spreading, may be monolayer, of the fine drug on the carrier surface. From this mechanism, increment of carrier content should increase the dissolution as the increase of total surface area and lesser agglomeration. However, no significant different in dissolution profile from the increase carrier ratio 1 to 3, this result may be due to the maximum increased dissolution profile was obtained in the lowest of carrier ratio.

The effect of carrier type on dissolution profile was investigated. Chitin and its derivatives, except CSU, showed superior than the comparative carrier PVP in the order : CT > CS > LMCS > PVP >> CSU. This technique did not include PEG because PEG BM could not be ball milled. Comparison among the carriers, although PVP BM showed the same drug crystal changed as other BM system. The disadvantage of PVP was considered due to the increased medium viscosity around the drug particle which would reduce the dissolution of the drug in diffusion layer. Therefore the dissolution achieved was lesser than those of chitin - milling technique.

In brief, all studied carriers yield dissolution profile satisfactory. For each carrier, the dispersion that obtained in the highest dissolution were in the order of : LMCS KM > CT BM > CS BM > PVP BM > PEG SM > CSU KM. On the other hand, for each methods obtained, the highest were in the order of : BM > KM > PM > for PVP, CT, CS ; SM > KM > PM for PEG; KM > SM > BM > PM for LMCS, CSU.

The possible mechanism for enhance dissolution profile of the studied dissolution could be explained by : The solid state changed of the drug ; decrease of crystallinity, partial and/or amorphous form, decrease crystal size/shape, particle size reduction, polymorphic transformation; and the effect of carrier ; improve of wettability, deaggregation, disintegration effect. These mechanisms were summarized in Table 7.

Tablet Evaluation

Based on the good performance of dissolution profile, nine of 1:1 HCTZ-dispersion mixtures were selected and subjected to prepare into tablet dosage form. The produced tablets, using direct compression method with basic formula, were compared with the two commercials tablets (Brand A, Brand B). The results showed the order of increased dissolution of tablet as follow : CT BM > CS BM > LMCS SM > LMCS KM > PEG SM > LMCS BM

Table 7 The possible mechanism of enhancing dissolution of HCTZ from various dispersions.

carrier	method	Mechanisms				
		Particle size reduction	Deaggregation Deagglomeration	Disintegrant effect	Improving of wettability	Changing crystallinity
CT	PM	-	+	+	+	-
	KM	+	+	+	+	0
	SMD	+	+	+	+	P_2+A_2
	BM	+	+	+	+	P_2
CS	PM	-	+	+	+	-
	KM	+	+	+	+	0
	SMD	+	+	+	+	P_2+A_2
	BM	+	+	+	+	P_2
CSU	PM	-	+	+	+	-
	KM	+	+	+	+	P_2
	SMD	+	+	+	+	P_2+A_2
	BM	+	+	+	+	P_2
LMCS	PM	-	+	-	+	-
	KM	+	+	-	+	P_2
	SM	+	+	-	+	P_3
	SMD	+	-	-	+	P_2+A_2
	BM (SW,VB)	+	-	-	+	P_2
PVP	PM	-	-	-	-	-
	KM	+	+	-	-	0
	SM	+	+	-	-	A_1
	BM	+	+	-	-	P_2
PEG	PM	-	+	-	+	-
	KM	+	-	-	+	0
	SM	+	+	-	+	P_4

Note : + positive
- negative
0 undone
A_1 Amorphous form
A_2 Partial amorphous form
P_1 Polymorph of HCTZ (main peaks at 19°,29° angle)
P_2 Polymorph of HCTZ BM (main peaks at 16.5° ,19° ,21° ,24.5° ,29° angle)
P_3 Another of HCTZ crystalline type (main peaks at 16.5 °,19° ,21° -22° ,29° angle)
P_4 Another of HCTZ crystalline type (main peaks at 21° ,23.5° angle)

(SW, VB) > PVP BM > CSU KM with the $t_{60\%}$ of 2.5, 3.12, 4.37, 4.68, 4.96, 5.62, 5.62, 25.31, > 1 hr, respectively.

Comparison of $t_{60\%}$ showed that commercial and prepared tablets except CSU KM met the USP XXII requirements (60% HCTZ dissolved within 1hr). The prepared tablets yielded far better dissolution than both commercial tablets (Brand A-24.4, Brand B-30 minutes) except PVP BM. Large differences in dissolution behavior among the prepared and commercial tablets was mainly due to the factor of HCTZ - carrier dispersion techniques. the other factors may be the difference in formula and method of tabletting due to the blank tablet also exhibited higher dissolution than the commercial tablets. However, it was clearly observed that dissolution of blank tablet was far lesser than the produced tablets, so the factor of different formula/method of tabletting can be omitted.

In general, the higher hardness of tablet the longer disintegration time and $t_{60\%}$ (Lowenthal, 1972). Although the compression force was fixed at 500 Ib the hardness obtained in each prepared tablets were different. This was due to the compressibility of each carrier in prepared tablets. The order of increased hardness was as follow: LMCS SM< LMCS KM<PEG SM<CT BM<CS BM<LMCS BM(SW, VB)<PVP BM. It was obvious that PVP BM possess the highest hardness of >10 kps while the other carrier gave lesser and were in the range of 4.5-8 kps. For disintegration time, the order was as follow: CT BM<CS BM<brand A<LMCS KM<LMCS SM<PEG SM< LMCS BM(SW, VB)<PVP BM<brand B. It was showed that the disintegration time was corresponding to the dissolution profile but not exactly to the hardness.

For the commercial tablets, brand A exhibited very fast disintegration. It was suggested that brand A might contain a superdisintegrant, similar to the prepared tablets, but not brand B. However, its dissolution profile was still far lesser than the produced tablets.

Due to the order of increased dissolution profile in dispersion mixture powder, it can be said that the order of increased dissolution in prepared tablets were accordingly to those of powder. Some differences were observed, tablets of CT BM and CS BM exhibited superior dissolution than that of LMCS KM. This was due to the same reason in powder dissolution. In contrast PVP BM tablet displayed slower dissolution profile than both commercial tablets. It may be explained by the binding property of PVP. Also CSU KM tablet failed to meet the USP XXII dissolution requirement , as the tablet swollen and retained in the basket more than one hour. This was due to the gel forming properties of chitosan in acid medium. Thus the reason that CS BM did not forming gel may

explained the ball milling technique reduced particle size and drug was deposited on its surface. While in kneading method, drug was wrapped in larger sheet of chitosan, when contact with the medium the drug was surrounded by wrapping gel.

As the in vitro results, it was indicated that ball milling of HCTZ with carrier LMCS, CT or CS and kneading or solvent method with LMCS improved the dissolution of HCTZ, suggesting that a similar enhancement can be expected for the other poorly soluble drugs in the same way. For carrier selection, LMCS was found to be an excellent carrier for improve dissolution profile. The highest dissolution and the shortest of $t_{80\%}$ from powder dispersions in Table 6 were observed in LMCS PM, LMCS KM, LMCS SM. CT and CS showed good performance in ball milling technique, but not CSU. It can be stated that CT was the best carrier as the good performance of increase dissolution with the lowest price compared to CS or LMCS. However, CS was the second choice of carrier as the same pattern of increased dissolution and the price was only slightly higher than CT. In consideration, if CSU gave the same characteristic as CS, it should be the selected one because it was the local material which would improve the local industry. This was clearly that chitin and its derivatives, with proper degree of deacetylation and molecular weight, can be useful for improvement of dissolution of HCTZ and more advantage than the popular carrier PVP or PEG. For method selection, kneading method was the best method simple and easy to prepare for improvement of dissolution, espectially with LMCS. The next chosen method was ball milling due to the effectiveness on improvement of dissolution profile in versatile carriers. Moreover, the understanding on its solid state characteristics should be considered, it can be used to explain why such dispersed products gave high dissolution or predict the outcome of the final product obtained. Dispersion method, type and quantity of carrier used also influenced on the drug quality and production cost.

In addition, further investigation should be participated with the stability of the test preparation and the in vivo test to make sure that no problems occur after the product has launched in the markets.

CONCLUSION

Chitin and its derivatives can be used to increase the dissolution of HCTZ via various dispersion techniques : KM can be used to prepare dispersion mixtures with all carriers studied ; SM and SMD were suitable for water soluble carriers and water insoluble carriers respectively ; BM was suitable for all carriers except PEG which could not be conducted. The types of carriers, including the amount used, influenced the dissolution of HCTZ from dispersion. The carriers, CT and CS, can improve drug dissolution effectively by BM technique, while CSU was not suitable for this technique. The following concerned carrier, LMCS, was the carrier suitable for most techniques. In addition, the solid state change observed by SEM, X-ray diffraction, IR spectra, and DTA studied was an important role for improving the dissolution characteristics. HCTZ in dispersions studied was changed through partially amorphous form, decrease in crystallinity and crystal size, shape, reduce in particle size, complexation or new polymorph. Another improvement was wettability and disintegrant properties.

From the investigation, dispersion mixtures which allow very much faster dissolution were CT BM, CS BM, LMCS KM, LMCS SM, PEG SM, LMCS BM. The results showed that chitin and its derivatives were more effective than the most common carriers of PVP and PEG. For prepared tablets, similar to powder systems, they showed superior than the two market HCTZ showed superior dissolution than the two marketed HCTZ tablets.