CHAPTER IV

RESULT AND DISCUSSION

Dissolution Testing Result

Pure Drugs

The regression parameter for dissolution data of the pure drug in pH 1.30 and 7.60 medium were shown in Table 11 and 12. Compared with the regression model from cumulative amount of drug release and square root time, the greater r^2 value and smaller s^2 were obtained from the regression model of cumulative amount of drug release and time. As discussed above, in both pH 1.30 and 7.60 medium, it could be considered that the regression model from drug release and time was more suitable for the dissolution data of pure compound than another model. Evaluated from the regression model, this representative equation provided a constant rate at all time which known as zero-order release pattern. Due to the influence of pH of the dissolution medium on the ionizability of drugs, except menadione, dissolution rate of the pure drugs in acid medium were different from the rate in alkaline medium. For instance, owing to unionizable nature of the acid drugs in pH 1.30 medium, as in Figure 20 and 21, dissolution rate in pH 1.30 medium of the two acid drugs, chlorpropamide and sulfamethoxazole, were prominently

lower than the rate in pH 7.60 medium. Conversely, the dissolution rate in pH 7.60 medium of the two basic drugs, haloperidol and perphenazine, were greatly lower than the rate in pH 1.30 medium as in Figure 22 and 23.

In contrary, because of its neutral character, dissolution rate of menadione was not affected by the pH of dissolution medium. As in Table 13, by means of student t test, the result from the slope parallelism test indicated that the dissolution rate of menadione in pH 1.30 and 7.60 medium were statistically indifferent at 95% confidence. This statistic outcome could be used to show the effect of pH on the dissolution rate of menadione.

On the other hand, as shown in Table 13, the unacceptable t value of griseofulvin indicated that the dissolution rate of griseofulvin in these two mediums were significantly different. As shown in Table 11 and 12, it was demonstrated that dissolution rate of griseofulvin in pH 1.30 medium was about 1.32 fold greater than the rate in pH 7.60 medium. This result corresponded with the solubility outcome of griseofulvin which expressed in Table 14 and 15. From these two tables, it showed that griseofulvin could be dissolved in pH 1.30 better than dissolved in pH 7.60 medium. Compared with the solubilizing properties in pH 7.60, the augmentation in solubility of griseofulvin in pH 1.30 medium was slightly different from the increasing in the dissolution rate in the same medium. The increment in the solubilizing

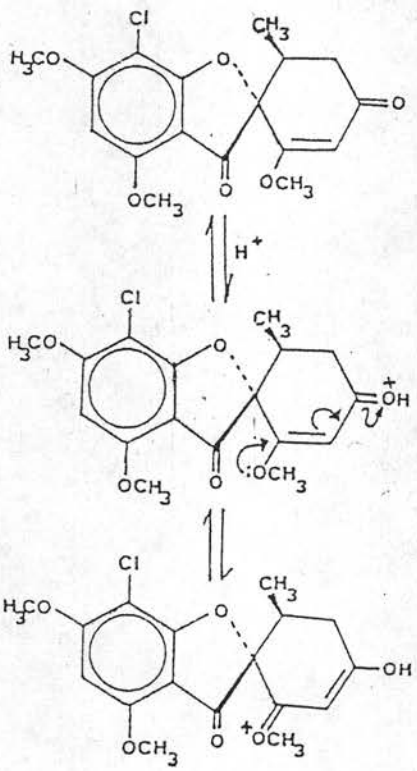
characters of griseofulvin in pH 1.30 medium, it was manifested that, dislike menadione, the other neutral molecule, pH of the dissolution medium influenced on the solubilizing properties of griseofulvin, as shown in Eq. 7 below:

$$pH = pK_a - \log \frac{[B]}{[HB^+]} \qquad \text{Eq. 7}$$

where, [B] : the concentration of nonionized form
and $[BH^+]$: the concentration of ionized form.

Calculated from the solubility of griseofulvin in pH 1.30 and 7.60 medium, the pK_a of griseofulvin was about 1.73 which is in good agreement with the solubility and dissolution result. Due to the increment in the total amount of griseofulvin in solution, the solubility and dissolution rate of griseofulvin in pH 1.30 medium is greater than the solubility and the dissolution rate in pH 7.60 medium.

The most likely protonation position is the 4/position of cyclohexanone ring by the high concentration of H_3O^+ in pH 1.30 medium. The possible protonation process was illustrated in Scheme 1 as followed.



Scheme 1 : The possible protonation process of 4'keto group in cyclohexanone ring of griseofulvin in pH 1.30 medium.

Mixtures of Cholic Acid : Drugs

When the drugs were mixed with cholic acid (1:1 w/w) in the form of physical mixture and glass mixture, the dissolution characters of these drugs were obviously changed as shown in Figure 26-49. This suggestion corresponded with the statistic outcome of the parallelism test in Table 16-19. As shown in these tables, the releasing rate of the drugs from the plane surface of the

pure compounds and their respective physical and glass mixture were statistical dissimilar. To define the effect of cholic acid on the dissolution rate of the drugs, the comparison of dissolution rate of the pure compounds with the rate of its mixture in the same medium was an essential tool. In this discussion, we would like to evaluate the effect of cholic acid on dissolution rate of physical mixture at first.

1. Physical Mixture

The regression parameter for dissolution profiles of physical mixture in pH 1.30 and 7.60 medium were displayed in Table 20 and 21. From the regression data in these two tables, the fitting model for physical mixture in each medium were unlike. As the statistic data in Table 20, leaving out griseofulvin, a greater r^2 value and smaller s^2 value were achieved from the regression model from cumulative amount of drug release and square root time whereas, the statistic data in Table 21 showed the opposite result.

From the result in Table 20, it could be concluded that, exception for griseofulvin, the regression model from the plot of cumulative amount of drug release and square root time was the best representative model for dissolution profile of physical mixture in pH 1.30 medium. As presented by Noyes-Whitney (Eq.1), the model obtained from this appropriated equation was known as matrix-

release pattern.

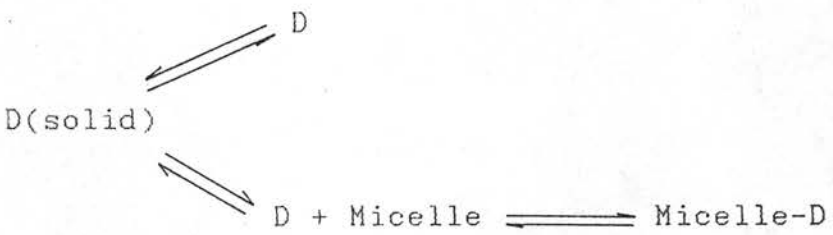
Due to the weak acid character of cholic acid, the solubility of cholic acid was limitted when placed into the pH 1.30 medium. At the beginning of the dissolution process, the drug dissolved and receded at the faster rate within the solid phase, leaving cholic acid layer at the solid surface. The matrix release profile was obtained from the diffusion of the inner drug through cholic layer before reach the dissolution medium. The occurence of the cholic acid layer at the outermost layer of the tablet could be confirmed by the results from calculation with Eq.3 in Table 22. As shown in Figure 26-27, 30-31, 34-35, 38-39 and 45-46 , not only the matrix release character were produced but also the dissolution rate of these mixtures were outstandingly diminished, when the cholic acid layer existed at the dissolution surface.

In opposition to the dissolution result of the other drugs shown in Table 20, the release of griseofulvin from physical mixture in pH 1.30 medium showed zero-order release pattern. Calculation with Eq. 3, summarized in Table 22, suggested that only griseofulvin was the outermost layer. As presented in Table 11 and 20 together with 16 and 17, the observed dissolution rate of pure griseofulvin was slightly higher ,but statistic significant, than its dissolution rate from the corresponding physical mixture. This phenomenon was often observed when the ratio of N_{CA}/N_D was closed to the ratio

of $C_{CA}D_{CA}/C_DC_D$ (45).

However, these characters were changed when the physical mixture was placed into pH 7.60 medium. As in Table 21, similar to dissolution profile of the pure drugs, a larger r^2 value and smaller s^2 was gained from the regression model of cumulative amount of drug release and time. As these results, it could be inferred that the zero order pattern was more suitable for dissolution data of physical mixture in pH 7.60 medium than the matrix released pattern.

Ionization constant of cholic acid was about 5. Hence, in pH 7.60 medium, more than a half of soluble form of cholic acid were in ionized form. Like other surfactant, in pH 7.60 medium, the micelle of cholic acid would enhance the dissolution rate of the drugs as shown in Scheme 2 below:



Scheme 2 : Micellar solubilizing mechanism

The concentration of free drug (D) was maintained at saturated level as long as we had the solid drug at the surface of tablet. The micellar solubilizing leaded to increase in total solubility of drug, resulting in higher in dissolution rate when compared to pure drug.

However, this phenomenon did not occur in the dissolution of the physical mixture of the acidic drugs, chlorpropamide, sulfamethoxazole. The reason was that, as shown in Table 24, there was the existance of cholic acid layer at the solid surface and the diffusion through the cholic acid layer was the rate determining step for the release of the acidic drugs from the physical mixture. The micelle formation in aqueous phase was unable to modify the diffusion rate through cholic acid layer. Thus, the dissolution rate of the acid drugs from the physical mixture was not affected by the micellar solubilizing of cholic acid in this medium.

The decrease in releasing rate from the physical mixture of the acidic drugs in pH 7.60 medium could be explained by the existing of cholic acid layer at the outersurface layer and thus the concentration of the drug molecule at the solid-liquid interface was below saturated concentration. As shown in Table 24, since the ratio of N_{CA}/N_D was closed to the ratio of $C_{CA}D_{CA}/C_DC_D$ ration, the cholic acid layer at the surface was possibly quite thin and this minute layer was too thin to modify the

dissolution pattern of the acid drug in this medium.

2. Glass Mixture

Figures 26-49 showed dissolution of drugs-cholic acid glass mixtures. The statistical analysis of these dissolution profiles were listed in Table 24 and 25. In both pH 1.30 and 7.60 medium, the statistical data manifested that the release of the drugs followed matrix release pattern, with the exception of perphenazine in pH 1.30 medium. Table 11-12, 16-17 and 20-21 showed that, exception for perphenazine in pH 1.30 medium, all of the dissolution rates from the glass mixture of each drug were lower than the rate of its respective pure compound and physical mixture in both pH 1.30 and 7.60 medium. These results suggested that there were the occurence of some possible interactions between cholic acid and cholic acid as well as cholic acid and drugs during the heating and/or cooling cholic acid and the drugs to form glass mixture and this intereaction may lead to the formation of less soluble compound which may form the matrix release pattern.

As shown in Table 18, the zero-order model was more suitable for the dissolution profile of the cholic acid-perphenazine glass mixture in pH 1.30 medium than the matrix release model. Compared with the dissolution rate in pH 1.30 medium of the pure perphenazine and its respective physical mixture, the dissolution rate of the

glass mixture showed the fastest rate since there was the rapid flaking of the solid surface.

Concisely, from the dissolution outcome, the releasing rate of the drug from the physical mixture and the glass mixture were regulated by the different factors. For physical mixture, the dissolution rate was controlled by the physical factors as the dissolving nature of both drugs and cholic acid in dissolution medium, the surface component at any time t and micellar solubilizing of cholic acid, while the releasing rate from the glass mixture was eminently governed by the possible interaction between the drugs and cholic acid or due to cholic acid-cholic acid interaction.

To provide more information about the possible interaction in the mixtures, IR spectroscopic method was used to determine the functional group that may be involved in this interaction. The discussion about the interaction by this appropriated method was expressed in the next section.

IR Spectrum Determination

Generally regarded as one of the method that provided unambiguous characterization of various molecular modifications, IR spectroscopic method was used to deliver more information about cholic acid-drug interaction. To get more information about this interaction, a comparative

study of the vibrational frequency of various functional groups in the three compounds, cholic acid, drugs and its mixture, were necessary. By the comparison, the noticably different character of individual band in the spectrum of the mixture could indicate the modification in these particular groups.

Cholic Acid

A. Crystalline Form of Cholic acid

IR spectrum of crystalline cholic acid was shown in Figure 50. There were five peaks that may be related to its steroid skeleton and methyl side chain. The first one, an intense doublet peak at 2950 and 2890 cm^{-1} associated with C-H stretching vibration of 24-carbon skeleton of cholan structure. Showing as rather broad peaks at 1470, 1450 and 1380 cm^{-1}, these three peaks probably related to C-H in plane bending of both methyl and methylene group in its steroid structure. Not only the hydrophobic skeleton but the hydrophillic structure as three hydroxyl and one carboxylic groups were also existed in cholic acid molecule. In this spectrum, these hydrophillic functional groups displayed their symbolic peaks in the adjoining region to the hydrophobic characterizing region. The region of hydroxyl group was the first range that would be pay attention to. In this region, extended from 3600 to 3000 cm^{-1}, there were three

O-H stretching peaks which showed the character of O-H bond in three hydroxyl and one carboxylic groups. An intense and sharp peak at 3550 cm^{-1}, the first symbolic peak was assigned to O-H stretching vibration of terminal free hydroxyl group. Next to this peak, a rather sharp peak at 3350 cm^{-1} was represented to the stretching vibration of three alcoholic hydroxyl groups existing in hydrogen bond formation. And the other peak at 3200 cm^{-1} was due to O-H stretching vibration of mixed hydrogen bond between alcoholic and acid hydroxyl groups.

Besides the O-H stretching peaks, these hydrophillic groups were also characterized by the coupling peak between C-O stretching and O-H in-plane bending. Ordinarily, these coupling peak would show their characteristic peaks as two medium peaks in the range from 1450 - 1200 cm^{-1}. However, because of the medium intensity of the O-H in-plane bending band, this peak was always obscurred by the CH_3 and CH_2 bending peak which showed its strong intensity in this region. In this manners, an easier determination peak, the C-O stretching peak was only used to identified this hydrophillic side chain.

Generally, the stretching peaks of C-O bonds in saturated cyclic alcohol were often met in the range from 1090 to 1020 cm^{-1}. Hence, the three rather sharp peaks at 1090, 1078 and 1040 cm^{-1} was possibly obtained from stretching vibration of the three alcoholic C-O bond.

A broad peak at 1240 cm^{-1} may be associated with C-O stretching vibration of carboxyl functional group which always presented in the range extended from 1300 to 1200 cm^{-1}. Together with the peaks of C-O and O-H stretching, the acid functional group also provided the characteristic peak of C=O bond. For cholic acid, the C=O bond showed a symbolic peak for its stretching character as a rather broad peak at 1720 cm^{-1}. In addition to the stretching peak of hydroxyl and carbonyl part, cholic acid showed its dimeric association character by a small peak at 915 cm^{-1}.

These results indicated that, in the cholic acid crystal structure, two or more molecules of cholic acid were joined together with the hydrogen bonding which may be accomplished by three alcoholic and one acidic functional groups. Along with the hydrogen bond formations, the peak of free O-H stretching at 3550 cm^{-1} indicated that, in cholic crystal structure, there was at least one free hydroxyl groups.

From the X-ray crystallographic study of Kunio Miki and collaborators in 1990, the complete feature of cholic acid crystal was presented (29). Figure 51 was the outcome of this study. From this figure, the rigid hydrogen bond network between four hydroxyl and one carbonyl groups was shown and this illustration was agreeable with the conclusion of the IR result.

B. Glass Form of Cholic acid

IR spectrum of glass form of cholic acid was demonstrated in Figure 52. Compared with the typical peaks in the spectrum of crystalline form, there were some alterntion showing in the spectrum of glass mixture. All of the modifications were listed in Table 26. As the results displayed in this table, almost all of the alternations were occurred in the typical peaks of hydrophillic functional groups. In the O-H stretching region, the three symbolic peaks in the crystalline form was superseded by an intense and broad peak at 3450 cm^{-1}. Moreover, the carboxylic C=O stretching peak of the amorphous solid was expanded and presented at about 10 cm^{-1} lower than the peak in the spectrum of crystalline form. Besides these two main peaks, all of the C-O stretching peaks were also expanded.

Resembling to the other glassy state compounds, the enlargement of most characteristic peaks were obtained from hydrogen bonding formation which primarily responsible for glass formation by preventing recrystallization (13). Furthermore, these modification, especially, the broadenning of all C-O stretching peaks and C=O stretching peak as well as the extinction of free O-H streching peak from the spectrum of glass form, indicated that the interaction in this form completely occupied all of the cholic hydroxyl groups and potentially

interacted with the acid functional group.

From the IR spectrum, it was clear that there was substantial intermolecular polar groups interaction between cholic acid molecules in glass state. This undoubtedly would lead to different dissolution rate of drugs from the glass mixture as compared to the physical mixture.

Drugs and Their Respective Mixture

1. Acidic Drugs

1.1 Chlorpropamide

A. Pure Chlorpropamide :

Chlorpropamide was the first drug that we would like to discuss. IR spectrum of this compound was displayed in Figure 53. Both of the hydrophillic and hydrophobic characteristics were also shown in the molecular structure of chlorpropamide. The hydrophobic character of chlorpropamide was demonstrated by five characteristic peaks as followed. The three intense and sharp peaks at 2980, 2950 and 2900 cm^{-1} were related to the stretching vibration of C-H bond in chlorpropamide molecule. Likewise, the sharp and strong peak at 1475 cm^{-1} was assigned to the C=C stretching in phenyl ring and the medium peak at 820 cm^{-1} of C-H out of plane bending showed p-substituted character of the aromatic ring.

In regarded to hydrophillic characteristics, the sulfonylurea group demonstrated its characteristic peaks in the three region of this spectrum. In the first region of this spectrum, N-H stretching region, this polar functional group showed two intense characteristic peaks at 3350 and 3125 cm^{-1} for its urea and sulfonamide N-H stretching character. Generally, in the IR spectrum of amide compound, the coupling between the stretching vibration of amide C=O bond and the in-plane bending mode of amide N-H bond, amide I and amide II always showed the two intense peaks in the range from 1700 to 1500 cm^{-1}. For chlorpropamide, both amide I and amide II peaks were shown as the two strong and rather broad peak at 1663 and 1550 cm^{-1}. In addition, the characteristic of sulfonylurea were also expressed by the two intense peaks at 1355 and 1160 cm^{-1} assigned to asymmetrical and symmetrical vibration of the sulfonyl group.

Existing at lower frequency than ordinary N-H stretching peak and exhibiting as a rather broad peak of sulfonamide N-H peak, it could be thought that the sulfonamide N-H part played an importance role in linking each of chlorpropamide molecules together with hydrogen bond.

Elucidated by Chung Hoe Koo in 1980 (46), the crystal structure of chlorpropamide from X-ray crystallographic determination was provided. It provided additional support to this suggestion. This evidence was

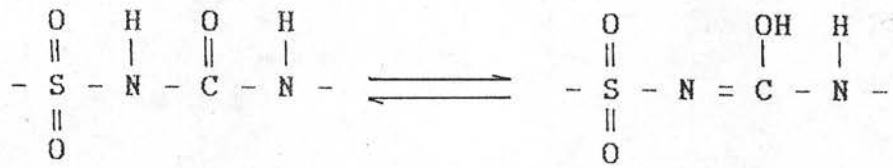
manifested that there was two kinds of hydrogen bond that holded the molecules together. These two bonds were formed between sulfonamide N atom and carbonyl O atom as well as between urea N atom and sulfonyl O atom. The recommended feature of hydrogen bond in chlorpropamide crystal was shown in Figure 54.

B. Physical Mixture : IR spectrum of physical mixture of chlorpropamide was displayed in Figure 55. Table 27 summarized the comparison of the IR spectra of physical mixture and its parent compounds, crystalline cholic acid and chlorpropamide. All of the characteristic peaks of each parent compound still existed in the spectrum of physical mixture at their respective positions. Some alternations in peak character, such as shape and intensity, resulted from the fusion of the typical peaks of cholic acid and chlorpropamide which placed in the same position or in the adjacent location. Corresponding with the dissolution testing result, this IR outcome indicated that the interaction between chlorpropamide and cholic acid molecules was not occured in this mixture. Consequently, the alternation of dissolution rate of physical mixture in both pH 1.30 and 7.60 medium could be ascribed by the existance of cholic acid layer at the outersurface layer of the solid phase.

C. Glass Mixture : In contrary, IR spectrum of glass mixture exhibited some different

characters of certain absorption peaks from its parent compounds, cholic acid and chlorpropamide, as in Figure 56. All of these alternation were summarized in Table 28. In view of cholic acid, we observed the far more broadenning and shift about 50 and 10 cm^{-1} to lower frequency of the characteristic peaks of both O-H and C=O bonds, respectively. This alternation was mentioned to the involvement of the carboxyl and hydroxyl groups of cholic acid molecule in the formation of cholic acid-chlorpropamide interaction.

Respected to the typical peaks of chlorpropamide, there were the absent of amide I and the shift of amide II peak from 1550 to 1540 cm^{-1}. These modification and the present of a new medium peak at 1580 cm^{-1} were implied that there was an occurence of enolization in sulfonylurea part of chlorpropamide as in Scheme II.



keto form enol form

Scheme II: keto-enol tautomerism of sulfonylurea part

In the range from 3500-3000 cm^{-1} of this spectrum, The stretching peak of hydroxyl group of the enol which was usually broad and shallow was not observed. The missing of this expected peak may be obtained from the possible overlap with the largely extended O-H stretching peak of cholic acid at 3400 cm^{-1}.

Due to rapid cool of the melted component in the glass preparating process, it was possible that there was partial transformation of keto form to enol form. This suggestion could be substantiated by the existence of sulfonamide N-H stretching peak as a medium peak at 3080 cm^{-1}.

Besides the modification in sulfonamide N-H peak, there were the shift to lower frequency of asymmetric stretching of sulfonamide S=O and sulfonamide N-H bond about 10 cm^{-1} and 45 cm^{-1}, respectively. These changes indicated to the involvement of both of sulfonamide sulfonyl and N-H part of chlorpropamide in the cholic acid-chlorpropamide interaction in glass mixture and it was quite possible that the enol form of chlorpropamide was involved in this interaction.

From the IR spectroscopy results, we could conclude that the interaction between chlorpropamide and cholic acid involved the polar functional groups of both molecules. Because of these interactions, cholic acid would turn its non-polar face toward the solvent phase

and thus resulting in lower dissolution rate of chlorpropamide from the glass mixture.

1.2 Sulfamethoxazole

A. Pure Sulfamethoxazole :

Sulfamethoxazole was the second drugs that we would like to discuss. IR spectrum of this compound was shown in Figure 57. Similar to other sulfa drugs, its sulfonamide character was expressed by three typical peaks. Corresponding with stretching vibration of sulfonamide N-H bond, the first symbolic peak displayed as a sharp and intense peak at 3300 cm^{-1}. Asymmetric and symmetric S=O stretching peak, the other two characteristic peaks of sulfonamide were observed as two intense peaks at 1368 cm^{-1} and 1160 cm^{-1}. In addition, the amino group existing in para position to sulfonamide group showed two coupling peaks, asymmetric and symmetric N-H stretching peaks, at 3490 and 3390 cm^{-1} and also N-H in plane bending at 1620 cm^{-1}. Besides the typical peaks of the hydrophillic functional groups, the phenyl and isoxazole were also displayed their symbolic peaks in the neighboring region. The phenyl and isoxazole ring showed a medium peak at 3150 cm^{-1} for their C-H stretching character and a several peaks in the range from 1600 to 1470 cm^{-1} for their C=C and C=N vibrational character. The study of Guillery in 1972 (47) revealed that the p-amino group, the acidic N-hydrogen atom and the oxygen

atom of S-O group were involved in the intermolecular hydrogen bonding in molecular crystal of sulfonamide, respectively. This reported was previously helpful to imaginate to crystal structural of sulfamethoxazole and the feasible hydrogen bond in the crystal structure of sulfamethoxazole were displayed in Figure 58.

B. Physical Mixture : IR spectrum of physical mixture of cholic acid-sulfamethoxazole compared with the spectra of its parent compounds, were shown in Figure 59 and summerized in Table 29. Similar to the physical mixture of cholic acid-chlorpropamide, the spectrum of the physical mixture was the sum of the individual spectra of its parent compounds. Therefore, the dissolution rate of this mixture were also depended on the solubility of cholic acid and sulfamethoxazole in the dissolution medium and the existence of cholic acid layer at the outermost layer of the solid phase.

C. Glass Mixture : In accordance with chlorpropamide outcome, the IR spectra in Figure 60 exhibited significantive difference between the spectra of glass mixture and its parent compounds. All of these IR variations were listed in Table 30. As shown in Figure 60, there were some modifications in the characteristic peaks of cholic acid and sulfamethoxazole in the 3500-3000 cm^{-1} region. The observed modifications were that the stretching peak of sulfonamide N-H bond of sulfamethoxazole and the O-H bond of cholic acid were broad

and shifted about 50 and 20 cm^{-1} to lower frequency, respectively, while the N-H stretching peak of 1^{o} part existed at its former position and showed slightly broader shape. It was difficult to with concluding any interaction involving 1^{o} amine since the change in the characteristic peak of 1^{o} amine was unconclusive.

Respected to the characteristic peak of sulfamethoxazole, besides the change in sulfonamide N-H stretching peak, The symbolic peak of S=O asymmetric vibration was absent from this spectrum. The missing of this peak may be achieved from the translocation and fusion with the peak at 1315 cm^{-1} to produce a new broad peak at 1320 cm^{-1}. These alternations manifested to the participation of the sulfonyl group of sulfamethoxazole in the cholic acid-sulfamethoxazole interaction.

All of these modifications indicated that there were the incident of interaction between sulfamethoxazole and cholic acid which occupied the polar part of each molecule, the sulfonamide group of sulfamethoxazole as well as hydroxyl groups and carboxylic group of cholic acid. Similar to the result of chlorpropamide, the lowest dissolution rate from glass mixture in each medium was appeared to be closely related to the effect of this interaction.

From the IR result of these two acidic drugs, there were polar-polar interaction between the carboxyl

and hydroxyl groups of cholic acid and the sulfonamide functional group of the acidic drugs. Considered to the modification in IR character of cholic acid in glassy state, it could be thought that besides the cholic acid-acidic drug interaction, the interaction between polar group of cholic acid in glassy state was also occurred in the cholic acid- acidic drug glass mixture. These polar interactionswould turn the non-polar plane of cholic acid to face the aqueous medium, and producing the reduction in dissolution rate from the glass mixture in both pH 1.30 and 7.60 medium.

2.Basic Drugs

2.1 Haloperidol

A. Pure Haloperidol : The IR spectrum of haloperidol was displayed in Figure 61. Aromatic ring and carbon skeleton of haloperidol showed their symbolic peaks in the two regions of this spectrum. In the C-H stretching region, the four peaks at 2990, 2930, 2850 and 2830 cm^{-1} represented to the stretching character of C-H bonds in carbon chain. In addition to the vibration of C-H bonds, C=C bonds in aromatic ring showed their stretching character as a group of four rather strong peaks at 1600, 1510, 1470 and 1410 cm^{-1} position.

Similar to other butyrophenone derivatives, C=O group of haloperidol was exhibited its particular peak as a sharp and intense peak at 1685 cm^{-1}. Another

hydrophillic part was in 4-hydroxypiperidine side chain. The hydroxyl group in 4-hydroxylpiperidine part showed its O-H stretching character by an rather broad band at 3150 cm^{-1}. The existing of this peak at lower frequency may arise from strong hydrogen bond formation. The X-ray crystallographic studied by many investigators revealed that the hydrogen bond in the haloperidol crystal was occurred between hydroxyl group in 4-hydroxypiperidine sidechain and N atom in piperidine ring (48-50).

In addition to these typical peaks, the rather broad band and moderate intensity and the sharp and strong intensity at 960 and 825 cm^{-1} may associate with the stretching vibration of C-O and C-Cl bond of haloperidol, respectively. The arrangement of haloperidol molecules in its crystal was exhibited as in Figure 62.

B. Physical Mixture : IR spectra of physical mixture of haloperidol and cholic acid was presented in Figure 63 and the conclusive IR result was displayed in Table 31. All of the characteristic peaks of crystal form of cholic acid, haloperidol and their combination peaks existed in their original positions. Consequently, the alteration in the rate of this mixture was regurated by the surface existing component and the micellar solubilizing nature of cholic acid.

C. Glass Mixture : Corresponding with the results from the acidic drugs, some of the

characteristic peaks were changed when they existed in spectrum of glass mixture. The IR spectrum of the cholic acid-haloperidol glass mixture and its parent spectra were displayed in Figure 64 and the alteration in character of the certain absorption peaks were noted in Table 32.

Respected to the characteristic peak of haloperidol, both of the O-H stretching and C-O stretching peak at 3150 and 960 cm^{-1}, respectively, were absent from this spectrum. The disappearance of these two typical peaks may accomplish by the translocation and combination with the other peaks in neighboring position. Compared with the uncombined peak at 950 cm^{-1}, the relative intensity of the peak at 980 cm^{-1} was rather high. From these observations, it could be considered that the missing of haloperidol C-O stretching peak may produce by the shift and merger with the peak at 980 cm^{-1}. Likewise, the absent of haloperidol O-H stretching peak may result from the shift and merger with the broad and intense peak of cholic acid in adjoining position. From these modifications, it could be considered that, probably, there was broken down of the strong intermolecular hydrogen bond in haloperidol structure and created a new bond which linked haloperidol and cholic acid molecules together.

Besides these changes, there were a great reduction in the intensity and shifted by 10 cm^{-1} to lower frequency of the haloperidol C-Cl stretching peak. Moreover, the C=O stretching peak of haloperidol showed great reduction in intensity with broaden shape in the former position. These changes showed the involvement of both chlorine atom and carbonyl group of haloperidol in the interaction between cholic acid and haloperidol in glass mixture.

In view of cholic acid, the characteristic peak of O-H stretching peak was shifted about 30 cm^{-1} to lower frequency. The modifications in some characteristic peaks of both cholic acid and haloperidol showed the possible hydrogen bond formation between chloro group of haloperidol and hydroxyl group of cholic acid.

Regarding to basic character of haloperidol, it was possible that, during the rapid cool step, there was partial formation of cholic acid-haloperidol salt in the glass mixture. This suggestion could be substantiated by an expanding and greatly reducing in intensity of cholic acid C=O stretching peak and displays as only a shoulder at the former position which in relation to the cholic acid C=O stretching peak in the spectrum of cholic acid-triethanolamine glass mixture, in Figure 65, and also the occurence of the shoulder peak at 1570 cm^{-1} which may associated with asymmetric stretching of cholate C=O stretching.

Concisively, there were two kinds of polar interactions among cholic and the drug molecules in the cholic acid-haloperidol glass mixture, hydrogen bonding and salt formation. From the dissolution results, the slowest rate was obtained from the dissolution of glass mixture in both pH 1.30 and 7.60 medium. This evidence manifested that the effect of hydrogen bond formation between cholic acid and cholic acid molecules and also between cholic acid and the drug molecules played a major role in controlling the release rate of the haloperidol from the glass mixture rather than the effect of salt formation.

2.2 Perphenazine

A. Pure Perphenazine : The second basic drug employed in the study was perphenazine. IR spectrum of perphenazine was shown in Figure 66. As in this figure, the hydroxyl group at the terminal of 2-hydroxyethyl piperazine side chain exhibited two medium and rather broad peaks at 3440 and 1030 cm^{-1} for the stretching vibration of O-H and C-O bond. Besides the characteristic peaks of the hydrophillic side chain, phenothiazine skeleton of perphenazine showed its symbolic peaks in the three regions of this spectrum. In the C-H stretching region, scoped from 2500 to 3000 cm^{-1}, the phenothiazine C-H bonds showed its stretching character at near 2940, 2880 and 2800 cm^{-1}. Moreover, the bending

vibration of these bond were presented as some medium intensity peaks in 1400 - 1300 cm^{-1} region. In addition, the C=C bond of this group showed its stretching character by three medium peaks at 1590, 1560 and 1450 cm^{-1}.

From the spectroscopic results, the character and existance of 2-hydroxyethyl piperazine O-H peak at lower frequency than ordinary O-H group indicated that this terminal hydroxyl group probably played importance role in the intermolecular hydrogen bond in crystal structure of perphenazine.

The X-ray crystallographic study by McDowell (51) could support this interpretation. From this report, it was manifested that the piperazine ring in perphenazine molecule was in chair conformation and a pair of perphenazine molecules were linked together with intermolecular hydrogen bond between hydroxyl H atom and piperazine N atom to build its crystal structure. Elucidated by McDowell in 1978, the crystal structure of perphenazine was shown as in Figure 67.

A. Physical Mixture : Figure 68 showed IR spectra of physical mixture of perphenazine and its parent compounds and Table 33 displayed conclusive results. As in Figure 68, there were no observable changes in the spectrum physical mixture. Corresponding with the result from the physical mixture of haloperidol, the releasing rate of perphenazine from this mixture was

also affected by the surface existing component and the micellar solubilization

B. Glass Mixture : IR spectrum of glass mixture was displayed in Figure 68 and the alternative characters were summarized as in Table 34. Respected to the characteristic peak of perphenazine, the modifications in the typical peaks of O-H stretching was unclear since it was obscurred by the merger with the strong intensity of cholic acid O-H strtching peak at the adjoining position. In addition, the three symbolic peaks of aromatic C=C stretching showed only little shift by 3 cm^{-1} to higher frequency. From these unconclusive results, it was difficult to determine any interaction involving perphenazine molecule.

Alternatively, in view of cholic acid, the more outstanding alterations were observed. From the IR spectrum, all of the modifications in peak character were only in the characteristic peak of the acid functional group. The stretching peak of O-H bonds was moved by 40 cm^{-1} from 3450 cm^{-1} to 3410 cm^{-1}. Moreover, compared with the uncombined C-O stretching peak at 1033 cm^{-1}, intensity of cholic C=O stretching peak was prominently decreased together with expanded shape. These changes were reflected to the involvement of the acid functionnal group of cholic acid in the creation of a new intermolecular bond in the cholic acid-perphenazine glass mixture.

Regarding to the basic character of perphenazine, it was possible that, during the rapid cool step, there was possible partial formation of cholic acid-perphenazine salt in the glass mixture. The suggestion about the partial salt formation in the cholic acid-perphenazine glass mixture could be substantiated by the decreasing and expanding of cholic C=O stretching peak of the cholic acid-triethanolamine glass mixture in Figure 65. As in Figure 65, not only the great reduction in intensity of cholic acid C=O stretching peak but also the two new peaks at 1578 and 1398 cm^{-1} which were responsible to asymmetric and symmetric stretching of cholate C=O bond were observed in this spectrum. For cholic acid-perphenazine glass mixture, due to occur in the same IR region of the typical peaks of perphenazine, these two symbolic peaks of cholate C=O stretching were merged by the original peaks. Compared with the uncombined peak at 1595 cm^{-1}, the increasing inrelative intensity of the peak at 1575 and 1400 cm^{-1} could be confirmed the exiting of the two symbolic peaks of cholate C=O bond.

The formation of cholic acid-perphenazine salt was processed through the carboxylic group of cholic acid and the tertiary amine part of perphenazine. Because of medium intensity and alway hidden by the stronger peak, it was difficult to define any changes in characteristic peak of C-N stretching. Thus, the discussion of alteration in the C-N stretching peak was not presented in

this chapter.

From the dissolution result, the releasing rate of perphenazine from the glass mixture was greater than the rate from the pure drug in pH 7.60 medium. This evidence indicated that, for perphenazine which had three basic functional groups, the release of perphenazine from the glass mixture was governed by the effect of salt formation rather than the effect of hydrogen bond formation between cholic acid-cholic acid in the glass mixture.

Conclusively, due to the basic character of the drugs, there was possible partial formation of salt between the basic drug and cholic acid during the heating and/or cooling process. The occurence of this suggested salt was corroborated by the IR spectrum of the cholic acid-triethanolamine glass mixture which showed the lower frequency shift of O-H stretching peak and also the expanding and far more decreasing in intensity of carboxyl C=O stretching peak.

Due to belonging three basic functional groups, the chance to form salt of perphenazine with cholic acid was greater than haloperidol which had one basic functional group. In relation to the effect of salt, dissolution rate of the pure perphenazine was slower than the rate of its glass mixture in both pH 1.30 and 7.60 medium.

In addition to the salt formation, the IR evidence indicated that there were hydrogen bond formation between cholic acid and cholic acid and also cholic acid and the basic drugs. Corresponding with the the dissolution result, the more basic functional groups, the greater effect of salt formation. Thus, we can observed the larger of salt formation in the dissolution of the cholic acid-perphenazine glass mixture which showed the faster rate than the rate of the pure perphenazine in both pH 1.30 and 7.60 medium. Likewise, the greater effect of hydrogen bonding was presented in the dissolution of the cholic acid-haloperidol glass mixture which showed the slowest releasing rate in both pH 1.30 and 7.60 medium.

3. Neutral Drugs

3.1 Griseofulvin

A. Pure Griseofulvin : IR spectrum of griseofulvin was displayed in Figured 70. Owing to moisture in the KBr crystal that used to prepare the IR sample, a weak broad band near 3460 cm^{-1} was shown in this spectrum. The stretching vibration of C-H bond was shown as a small peak at 2950 cm^{-1}. The two carbonyl groups of griseofulvin were demonstrated as two sharp and intense peaks at 1710 and 1658 cm^{-1}. The stronger peak at 1710 cm^{-1} was ascribed to the stretching vibration of C=O bond at position 3 in benzofuran ring while, the other peak at 1658 cm^{-1} attributed to the stretching vibration of C=O

bond in cyclohexanone ring.

In the next region, extended from 1620 to 1500 cm^{-1} ,both aromatic and alicyclic ring showed its unsaturated characters by a group of three peaks located at 1620, 1600 and 1580 cm^{-1}. The ether linkage showed its characteristic peak as a medium and rather broad band at 1140 cm^{-1}.

The X-ray analysis studies by Brown and Sim (1963) (52) manifested that the intermolecular contact in griseofulvin crystal corresponded to normal Van der Waals interaction.

B. Physical Mixture : Figure 71 showed IR spectra of physical mixture of griseofulvin and its parent compounds. Resembling to the other drugs that discussed previously, the alterative characters were not observed in this spectrum. Thus, it could be considered that the releasing rate of griseofulvin from this mixture was affected by compositions of cholic acid and griseofulvin at the surface of solid phase and micellar solubilizing of cholic acid.

C. Glass Mixture : The spectra of cholic acid, griseofulvin and their glass mixture were displayed in Figure 72. The conclusive resultswere shown in Table 36. As shown in Figure 72, there were only unimportant shift of the typical peaks of cholic acid and griseofulvin. The characteristic peak of cholic O-H

stretching mode was moved by 10 cm^{-1} and also, cyclohexanone C=O steching peak of griseofulvin was shifted from 1655 cm^{-1} to 1648 cm^{-1}. From these modifications, it could be believed that there were the occurence of weak interaction between cholic acid and griseofulvin in this mixture.

Thoughtfully, it could be believed that this weak bond was not only one factors that could deteriorated the releasing rate of griseofulvin from the glass mixture in both pH 1.30 and 7.60 medium. From the existence of polar and non polar part face in the opposite plane of cholic acid and the incident of polar-polar interaction in the glass form of cholic acid, it could be considered that the cholic acid-cholic acid interaction was probably one of the other factors that affected the dissolution rate of the glass mixture.

3.2 Menadione

A. Pure Menadione : The last drug that we would like to discuss in this section was menadione. IR spectrum of menadione was shown in Figure 73. Similar to griseofulvin, a weak broad peak at about 3460 cm^{-1} may be bring about the moisture in the KBr crystal. Owing to have eleven carbon atom, the C-H stretching was expressed as a small peak at 2920 cm^{-1}. In the C=O strteching region, a sharp and intense peak at 1668 cm^{-1} associated with the stretching vibration of the

two carbonyl groups at 1,4 position of menadione. Existing at the adjoinning region, the three medium peaks located at 1625, 1620 and 1595 cm^{-1} represented to skeleton vibration in naphthaquinone ring. In addition to these characteristic peaks, a medium peak at 775 cm^{-1} could be used to indicated the ortho substitution pattern in the naphthaquinone ring.

Although the molecular arrangement in menadione crystal had never been demonstrated by any investigators, the crystal structure of 1,4-naphthaquinone and other derivatives were manifested by many sciencetists. Elucidated by Thozet and Gaultierin 1978 (53), the X-ray crystallographic study of 1,4-naphthaquinone showed that each of the naphthaquinone molecules were linked together by normal Van der Waals force to form its crystal structure. Likewise, the 5-chloro-1,4-naphthaquinone molecules were built their crystal structure by the help of Van der Waals interaction (54). In this manner, it was potentially guessed that the molecules of menadione used this non-polar interaction to hold them together.

B. Physical Mixture : IR spectrum of physical mixture of menadione was shown in Figure 74. As like the IR character of griseofulvin, the characteristic peaks of its parent compounds and their combinations were still presented in the spectrum of physical mixture. The unmodified character demonstrated that the dissolution rate of physical mixture was affected by the surface

existing component and micellar solubilizing of cholic acid.

C. Glass Mixture : IR spectrum of glass mixture was demonstrated in Figure 75 and all of the alternated characters in the spectrum of glass mixture were summarized in Table 38. As displayed in Figure 75, in the spectrum of glass mixture, There was only little shift of quinone C=O stretching peak from 1668 to 1665 cm^{-1}. From the unconclusive modification of this peak, It was difficult to define the interaction associating with menadione and cholic acid. It could be considered that the reduction of the releasing rate of menadione from its glass mixture may be accomplished by the formation of cholic acid-cholic acid interaction which would turn its non-polar face toward the dissolution medium.

Conclusively, the release of the neutral drugs from their respective glass mixture were controlled by the polar interaction among cholic acid molecules rather than the interaction between cholic and the drug molecules. This suggestion colud be confirmed by the unconclusive modification in IR character spectrum of cholic acid-neutral drug glass mixture.