CHAPTER V

DISCUSSION AND CONCLUSION

Preliminary investigation on sustained release diclofenac sodium microtablet

The main objective of this study was to prepare sustained release diclofenac sodium microtablets which had much smaller size than general tablets. Microtablets had 2-3 mm diameter and could be prepared by either direct compression or wet granulation method. The machine could be the single-punch rotary tabletting machine with special punch and die (Kolter et. al, 1997; Pich et. al, 1989). In this research, the special punch had three concave punches per punch holder and diameter of each special punch was 2.5 mm. Therefore, the physical properties of powder, especially the flow property was the necessary factor to produce microtablets with small diameter punches. The suitable formulations and production techniques were sought for producing powder met the requirement for microtableting.

Before proceeding with the sustained release diclofenac sodium microtablets, the compressible properties of diclofenac sodium were examined by classifying powder into three types. They were the untreated DS powder, the milled DS powder and the sieve DS powder. Conventional DS powder was available as a relative large particles. The reducing of particle size of DS powder was performed and offered to potentially increase the binding capacity (Pollock et al., 1996). Theoretically, the compressibility of powders and their strength depended on many factors, especially mechanical interactions between particle, such as, the contact area and particle bonding. Decreasing particle size of powder increased contact surface area between particle and increased bond formation of tablet. As a result, the compressibility could be improved (Dasei et al., 2001; Banker et al., 1991; Heistand et al., 1991). In this study, there should be an increase in the contact surface area by either sieving or milling, which would improve the compressibility of powder. However, it was found that the compressibility of each type was similar. Therefore, the original diclofenac sodium was chosen because of economic and ease of production.

The preliminary investigation on suitable diluent was investigated by various parameters. It was found that Ludipress and lactose were suitable diluents for production of microtablets. Both materials could improve flowability of powder mixtures in preliminary formulations that could be confirmed by two parameters, which were flow rate and angle of repose. Comparison to lactose, it appeared that Ludipress showed better flowability. Ludipress was spray-dried lactose that was granulated by spray drying techniques and used 3.5% povidone K-30 as binder and 3.5% crospovidone as disintegrant. Therefore, Ludipress had spherical shape and narrow size distribution that resulted in good flowability (Baykara et al., 1991; Goto et al., 1999). Whereas lactose was crystalline particles with irregular shape (Arthur et al., 2000). Hence, Ludipress could improve flowability over lactose (Banker et al., 1991). On contrary, the flow rate of other additives, such as, corn starch, tapioca starch and Era-tab could not be detected by the flow meter. Moreover, their results of angles of repose were correlated to their results of flow rate. Banker et al.(1991) reported that when starch was used in a direct mixing system, sticking and adhesion of powder at the wall of funnel of the flow meter were resulted. Because these diluents as the commercially available starch USP were hygroscopic and rapidly absorb atmospheric moisture. They may vary in high moisture content between 11% - 14%. It was found that Era-tab had the best flowability that compared with corn starch and tapioca starch. Because Era-tab was spray – dried rice starch that had a spherical shape and narrow size distribution. Both corn starch and tapioca starch showed similarily flowability that could be confirmed by their angles of repose.

The compressibility of both Ludipress and lactose were also satisfactory from the results of hardness and the percentage of friability. Comparison to lactose, it appeared that ludipress produced harder tablets. This was due deformation mechanism of Ludipress. Because Ludipress had a high level of amorphous lactose that compared with lactose. Therefore, the deformation mechanism of Ludipress was plastic deformation, resulting in hard tablet (Banker et al., 1991; Goto et al., 1999). Because the change of shape of tablet did not recover when the stress into tablet was released after complete compression. Moreover, the other diluents could not be compressed because their powder mixtures could not pass though hopper to die of tabletting machine. In addition, most properties of starch were unsatisfactory, especially poor binding property because of high moisture contents in starch.

Hence, the tablets that contained starch were often soft and difficult to compression (Banker et al., 1991).

The primary investigation on suitable formulations of sustained release diclofenac sodium microtablets was studied by the use of cellulose derivatives. Gradual adjustment of proportion of drug and cellulose derivatives had been formulated in attemps to achieve controlled release the drug. The optimal formulation and method should have good properties, especially flowability that was an important factor for preparing microtablet. Good flowability of powder had many advantages for microtablet production that could be summarized as follows: (US. Patent, 1981: 4,274,286)

- The powder easily flows in the hopper without forming air pocket
- The die cavity was filled more efficiently, and this was reflected in an increase of the mean of tablet weight and a decrease of the coefficient of variation, due to lack of low dosing.
- As a consequence of the uniformity tablet weights and uniform doses of active ingredients, also other parameters of the finished tablets, such as hardness, friability, disintegration time, dissolution test, and plasma level are reproducible. Another consequence of more efficient die cavity filling would be reflected in the uniformity of the compressing powder.
- Moreover, the high production rate was allowed by the high flow rate of free-flowing powder.

In addition, it should have good compressibility and could sustain the drug release. This study was an experimental design that depended on the amount of drug per one microtablet, concentrations and type of cellulose derivatives, production methods, the amount of filled microtablets in capsule and capsule size.

1. The preliminary investigation on suitable formulation and method for preparing microtablets which filled into capsule size NO. 3

All formulations with direct compression method could not be compressed because their powder mixtures could not flow pass through the hopper. Various parameters indicated

the poor flowability of these powders. It was found that their angles of repose were more than 30° and the flow rate could not be determined because the powder mixtures could not pass through the orifices of the funnel. The flowability of HPMC formulations was very poor because DS and HPMC had high adhesion property (Arthur et al.,2000; Adeyeye et al., 1990). DS and HPMC absorbed moistured from the atmosphere resulting in adhesion and sticking to wall of the funnel. Both materials were micronized particles that were less than 64 μm resulting electrostatic charge might be occurred. Moreover, DS was crystalline with irregular shape and HPMC was of fibrous or cylindrical shape (Arthur et al., 2000). Therefore, DS and HPMC showed poor flowability. In this study, there was a large amount of DS in these formulations when they were mixed together that resulted decreasing flowability of the powder mixtures (Cheng et al., 1993; Timmins et al., 1991). As a result, the powder mixtures adhered to the wall of hopper and densily packed into the hopper, which obstructed flowability of powder mixtures then pass through hopper to die of microtablets (Jame et al., 2000).

Comparison to the HPMC formulations, it appeared that the EC formulations showed better flowability. Because HPMC' s particle shape was fibrous or cylindrical whereas EC was of rod or round shape (Arthur et al., 2000). In addition, high adhesion property of HPMC due to hygroscopicity and electrostatic charge of micronized particles (Arthur et al.,2000; Adeyeye et al., 1990). But the powder mixtures of EC formulations also could not pass through the hopper that was similary to the HPMC formulations. Although, EC show good flowability, high binding capacity but its quantity was not enough to improve flowability of powder mixtures. As a result, the adhesion of powder mixtures to wall of hopper still be occurred (Desai et al., 2001;Ghaly et al.,1996; Upadrashla et al., 1993). On contrary, all formulations had narrow size distribution that was almost in 180 μm. It was in contrast to other flowability parameters. In general, narrow size distribution indicated good flowability of powders (Fassihi et al., 1987; Flemming et al., 1995). As a result, the particle size of each material was in the same range but the characteristics of each material, especially DS and HPMC showed high adhesion and poor flowability that caused poor flowability of powder mixtures and segregation after mixing.

All the wet granulation formulations could compressed into microtablets. The flowability of granules was much better than that of powder mixtures. Therefore they could

be further investigated. It was observed that their angles of repose were less than or equal to 30° and their flow rate were high. The wet granulation method could improve the properties of powder with regarding to tabletting, such as, enlargement the particle size and improvement flowability of powder. Moreover, the compressibility of powder was improved due to added binder, which coated the individual powder particles. Therefore the individual powder particles adhered to each other. As a result, it could be formed into agglomerates. In addition, wet granulation could prevent segregation of components of a homogeneous powder that mixed during processing, transferring and handling (Sheth et al.,1991). Therefore, the desirable properties of granules depended on several factors. One of all factors was the process of wet granulation.

In this study, the wet mixing process in the HPMC formulations (Formulation WGHCL and WGHCH) was different that affected to the obtained granules. The formulation contained with low content of HPMC (Formulation WGHCL), which used as a 20% w/w binder solution were mixed with the drug substance and the other component. The obtained damp mass was rubbery. The influence of HPMC as binder solution could be interpreted that the hydrophilic polymer presented in the blend were fully hydrated and bound with DS and other additives in the granulation stage. The obtained granules was partly agglomerated particles and partly segregated particles between DS sodium and HPMC, because HPMC solution could not uniformly spread and bind with all particles in the granulation stage (Timmins et al., 1991; Ping et al., 1996). After drying process, the obtained granules were strong because DS and soluble components in the mass could be dissolved in binder solution and recrystallized or precipitated during drying (Timmins et al., 1991). In addition, these component may be changed to amorphous form. Therefore, it necessarily used much force for dry sieving process that resulted fine particles were increased.

Formulation WGHCH that contained high content of HPMC had two variables that were different from the formulation WGHCL. They were the amount and addition method of HPMC. The amount of HPMC in formulation WGHCH was more than that in formulation WGHCL. HPMC was used half as a diluent and another half as a binder. The hydration of HPMC may not be uniform. HPMC as a binder solution was fully hydration whereas HPMC as a diluent would hydrate when contacted with solvent in the granulation stage. Therefore, the binding property of the latter portion with drug substance was slower

than that as binder solution. The obtained damp mass was likely to separate to be two parts. The first part was agglomerated particles that were sticky like rubber and another part was segregated particles of DS, HPMC and other components. The obtained granules were stronger than formulation WGHCL after drying process. Because increasing the amount of HPMC increased the hydration mechanism of HPMC that resulted in enhanced strong interparticulate bonding. Moreover, DS could dissolve to a greater extend on granulating fluid level that were devided as binder solution and as solvent during the granulation stage. As a result, the obtained granules were stronger than formulation WGHCL after drying process (Guojie et al., 1995; Timmins et al., 1991). The force for milling granules of formulation WGHCH was higher than that of formulation WGHCL. The result was an increase fine particle. Although, their characteristics of granule from both HPMC preparations were not good due to plenty of fine particles, but they could be compressed into microtablets.

Theoretically, if the amount of fine particle were high, the weight and drug content would be varied. In contrast, the weight variation of most obtained tablets was within acceptable limits, reflecting the favorable flowability that conferred by the wet granulation procedure (Cheng et al., 1993). Moreover, the single punch tabletting machine had low speed of 155 tablet/minute that would not affect to weight variation because slow press speed increased time intervals for the upper punches to enter into the die cavity. Therefore, feed shoes had enough time to uniformly fill the granules into all die cavity (Katikaneni et al., 1995; Wray, 1992).

The formulation WGEC that contained EC had same quantity and wet mixing process as the formulation WGHCH. The characteristic of the obtained damp mass was also undesirable because of the influence of EC that was used as binder solution and diluent. EC as a binder solution could disperse the polymer around other particles as a thin film. This would effectively hold particles together as granules and the dried film bonded granules to form tablet. Whereas EC as a diluent was dispersed and formed film bond with other particles by van der waals force during the granulation stage. Therefore, its binding action was not uniform. As a result, the obtained damp mass still separated to be two parts. The first part was agglomerated particles that were sticky but it was less than HPMC formulations. Because HPMC contained active functional groups such as hydroxyl groups that may be strong interacted with DS or other excipients in the formulation. Whereas, EC

contained ethoxy functional groups with a far lower tendency to react with DS and other excipients (Desai et al., 2001; Sarat et al.,1996). Therefore, bonding property of EC was weaker than that of HPMC. Another part was segregated particles of DS, EC and other additives . Therefore, it was easier to pass though the wet and dry sieving process. Moreover, broad size distribution occurred that was in a range of 250-500 μm. It may be due to segregation of mixing. However, the results of weight variation were within acceptable limits. It was due to low speed low speed of tabletting machine that affected to uniform filling of granules from feed shoes into die cavity as previously mentioned (Wray, 1992).

For all wet granulation formulations, the percentage drug content did not pass specified in official standard USP XXIV. This was due to inhomogeneous mixing during the granulation stage. For the HPMC formulations, HPMC content was the predominant controlling factor (Hogan et al., 1989). An increasing HPMC content decreased the percentage drug content. Because HPMC contained active functional groups such as hydroxyl groups with may be strong bound with DS (Desai et al., 2001). Moreover, the swelling structure of HPMC was gel barrier like network. DS would be trapped into the network of HPMC (Guojie et al., 1995; Hogan et al., 1989; Wray, 1992). Therefore, increasing HPMC content increased HPMC molecules to trap and bind with DS that resulted in decreased diffusion of drug from HPMC microtablets (Desai et al., 2001; Sarat et al., 1996). Comparison to HPMC microtablets, it appeared that EC microtablets showed higher the percentage drug content. Because EC contained ethoxy groups as active functional group that was further than hydroxyl groups (Arthur et al, 2000). Therefore, the binding property of EC was weaker than that of HPMC. In addition, EC was bind loosely with van der waal force between EC particles and other particles (Desai et al., 2001; Sarat et al., 1996). Hence, there were pores between particles. As a result, DS was easier to diffuse from EC microtablets than HPMC microtablets (Desai et al., 2001; Norma et al., 1997; Shan et al., 2001; Wray, 1992).

2. The preliminary investigation on suitable formulation and method for preparing microtablets which filled into capsule size NO. 2

Since the quantity of components in formulations were different from those of formulations for capsule size NO.3 due to the capsule size was changed to be a bigger size. As a result, increasing the amount of filled microtablets in capsule decreased the amount of drug per one microtablet and increased the amount of both cellulose derivatives. Therefore, it could improve efficacy of sustained drug release action in the formulations.

Both direct compression formulations (Formulation DHC and DEC) could be compressed into microtablets. Their flowability of powder mixtures were better than that of powder mixtures of capsule NO. 3. The amount of DS was decreased in the proportion ratio with Ludipress and HPMC of powder mixtures. Therefore, Ludipress, which had good flowability became to be a predominant factor to improve flowability. Because Ludipress had good properties such as spherical shape, free flowing (Baygara et al., 1991; Goto et al.' 1999; Banker et al., 1991; Jame et al.,1985).

Comparison to the formulation contained with HPMC, it appeared that the powder mixtures with EC showed better flowability. Because of EC's characteristic had good flowability. Therefore, the synergism of EC and Ludipress improved flowability of powder mixtures (Banker et al., 1991; Pruthvipathy et al., 1995). Moreover, the size distribution of both formulations that was in the same range of 180 μm.

Both direct compression formulations could compress to be desirable microtablets such as good hardness and uniformity of weight. Comparison to the HPMC formulation, it appeared that the EC formulation obtained harder microtablets. Because the plastic deformation was the predominant mechanism of EC to compacted after compression (Wray et al., 1992). This deformation was defined, as the change of shape of tablet did not recover when the stress into tablet was released after complete compression. Whereas the elastic deformation was the predominant mechanism for HPMC (Dasai et al., 2001; Kantikaneni et al., 1995; Shan et al., 2001; Upadrashta et al., 1994; Wray, 1992). This deformation was the change of shape of tablet recovered when the stress into tablet was released after complete

compression (Wray et al., 1992). In addition, the compression force affected to hardness of microtablet. Therefore, EC would provide denser microtablets than HPMC.

For wet granulation formulations the wet mixing process that was different from the formulations of Capsule NO.3 prepared by spraying the solvent pass though the nozzle on the drug-diluent mixture until suitable damp mass had been occurred. It was found that if water were added by spraying onto a stirred powder, agglomeration and lumps would be avoided. Because molecules of HPMC and EC were gradually changed when exposed to the granulation fluid. HPMC molecules in the mixture were gradually hydrated during the granulation stage. Both the increase in fluid available and the extending of mixing time were enable complete hydration. This would enhance uniform mixing and bonding between drug and other additives (Cheng et al., 1993; Timmins et al., 1991). Morover, the granulation fluid could disperse EC around other particles as a thin film. This could hold other particles together as granules (Cheng et al., 1993; Desai et al., 2001). Therefore, the mixing and binding of both HPMC and EC with DS were uniform than those of wet granulation formulations of Capsule NO. 3. These obtained granules had good properties, especially flowability. Their angles of repose were less than 30° and their flow rate were high. Moreover, increasing the amount of HPMC decreased flowability. Because increasing the amount of HPMC increased the amount of granulation fluid to hydrated molecule of HPMC and formed granules with other particles that resulted in increased interparticulate bonding. Therefore, increasing dissolution and recrystallization during drying of DS. The obtained granules were very strong. As a result, the amount of fine particles was increased that affected to poor flowability (Aithal et al., 1993; Timmins et al., 1991).

On contrary, increasing the EC content resulted in an increase in EC particles around other particles. The space between particles was decreased (Aithal et al., 1993; Desai et al., 2001; Herbert et al., 1991). The obtained granules were condenser granules than granules of HPMC formulations. Therefore, fine particles and broad size particle distribution could be still obtained. All wet granulation formulations could be compressed into microtablets. The obtained microtablets had good physical properties such sufficient hardness, acceptable weight and content uniformity. Comparison to the HPMC formulation, it appeared that the EC formulation produced harder microtablets. It was due to deformation of the material in compression process. Because the plastic deformation was the predominant mechanism of EC to compacted after compression whereas the elastic deformation was the predominant

mechanism for HPMC (Dasai et al., 2001; Kantikaneni et al., 1995; Shan et al., 2001; Upadrashta et al., 1994; Wray, 1992). Therefore, the deformation recovery of EC was not occurred that contrasted with HPMC. In addition, the compression force affected to hardness of microtablet.

Moreover, increasing HPMC content decreased hardness whereas increasing EC content did not affect the hardness of EC microtablets. The latter affected to friability and tendency of capping. Because increasing HPMC content resulted in increased elastic deformation after compression. Therefore, the deformation recovery was increased resulting in decreased hardness of microtablets (Aithal et al., 1993; Herbert et al., 1991; Wray,1992). On the contrary, increasing the EC content resulted in harder but also less friable and less prone to capping. Because increasing the EC content increased contact area with EC and increased bond formation. This greater interparticulate bond resisted the elastic rebound of the particles during the decompression and ejection (Aithal et al., 1993; Banker et al., 2001; Katikaneni et al., 1995). In addition, the hardness of microtablet depended on the compression force of tabletting machine.

The weight variation of all of direct compression and wet granulation formulations was within acceptable limit because low speed of 165 tablet sper minutes of the tabletting machine would not affect to weight variation. Because slowing press speed increased time intervals for the upper punches enter into the die cavity. Therefore, feed shoes had enough time uniform filling the granules into all die cavity (Katikaneni et al., 1995; Wray, 1992).

The percentage of drug content of both formulations passed the specification in USP XXIV. Comparison to the HPMC formulation, it was observed that the EC formulation showed higher percentage of drug content. This was due to binding properties of HPMC and EC that were related to the functional groups and their structure of HPMC and EC when exposed with medium as previously mentioned (Arthur et al., 2000; Desai et al., 2001; Sarat et al., 1996). Eventhough, the percentage of drug content passed the specification but the content uniformity did not pass. It was due to segregation of powder mixture after mixing. As a result, the drug content per microtablet was not uniform (Banker et al., 1991).

All microtablets frome wet granulation showed the percentage drug content and content uniformity passed the specification in USP XXIV. This was due to uniformity of mixing, good properties of granules such as flowability and compressibility.

The drug release behaviors

All release patterns of microtablet from all wet granulation formulations in capsule NO.2 were characterized by a smooth convex curve without an inflection point. The release rates of these microtablets were relatively fast at the initial stage, followed by a stage with decreased rate. In this study, it could observe that the drug release behaviors depended on type and concentration of cellulose derivatives.

The release patterns of diclofenac sodium from EC formulations showed that the drug was released from microtablets more slowly with an increase in ethylcellulose content. Therefore, adjusting the ethylcellulose contents in the microtablets could modify the release rate of drug. When the microtablets were brought in contact with water, a series of mass transport phenomena occurred. First, the pores near the surface of the matrix were filled by water and initial drug diffusion was controlled by the dissolution of the solute in the water-filled pores and by its continuous diffusion in water (Gurny et al., 1982; Katikaneni et al., 1995; Patomchaiviwat, 1993; Shan et al., 2001). Increasing the amount of EC increased hydrophobicity of EC, decreased diffusion and dissolution of water and drug that passed through the pores near the surdace of microtablets (Bain et al., 1991;Katikaneni et al., 1995; Patel et al., 1992; Shaikh et al.,1987). As a result, the release rate decreased for formulation WECL and WECH.

A visual inspection of the release profiles from the formulation WHCL and WHCH revealed a similar model. The drug release was observed to greater in pH 6.8, and lesser in 0.1 N. HCl. The solubility of diclofenac sodium (Pka = 4.0) was depent on pH. In 0.1N HCl medium, DS was neutralized with hydrogen ion and precipitated on or in the matrix. Therefore, almost DS was not in solution. Whereas DS could dissolve in phosphate buffer pH 6.8 and almost drug was in this medium (sheu et al., 1992).

The following stages could be involved in the release process from this system :

1. Hydration /penetration of the matrix by the dissolution fluid
2. Gelation at the outer layer of the matrix
3. Dissolution of the drug in the gel
4. Diffusion of drug through the gel layer
5. Slow dissolution of the outer most gel layer

Any or a combination of these could be a rate-limiting step in the process.

The diffusion of dissolution fluid through the gel was affected by the gel strength (Ping et al., 1995). The protective or barrier gel was in turn, controlled by the viscosity and amount of polymer used. Therefore, as expected, there was an inverse relationship between HPMC concentration and the rate of release. An increasing level of HPMC increased HPMC molecules to form gel when exposed to the fluid medium. Therefore, the gel formed was firmer and more cohesive. This resulted in slower drug release (Bain et al., 1991; Guojie et al., 1995; Hogan, 1989; Ping et al., 1995). On the other hand, an increase in the HPMC concentration would also increase the viscosity of the surrounding fluid, which would increase the gel-strength, and thus would slow the permeation rate of both the dissolution fluid, and the drug through the gel layer.

EC formulation showed higher the percentage of drug release than HPMC formulation. Because the structure of HPMC was gel layer formed, which was firm and strength (Bain et al., 1991; Hogan, 1989, Ping et al., 1995) whereas the structure of EC was porous and loose binding when exposed to the fluid medium (Shan et al., 2001). Therefore, the diffusion of drug substance of EC formulations was easier than that of HPMC formulations.

Identification of the sustained release diclofenac sodium microtablets

Spectrophotometric analysis by an infrared spectrophotometer, powder analysis by a differential scanning calorimeter of the microparticles were conducted to physicochemically identify the crystals of diclofenac sodium were mixed with the cellulose derivatives.

IR spectra of diclofenac sodium microtablets with various amounts of cellulose derivatives in the formulations showed a broad peak of cellulose derivatives at 1000-1200 cm^{-1}. This partly impaired the identification of the microtablets. The characteristic bands of diclofenac sodium appeared at 747, 767, 1284, 1306, 1506 and 1575 cm^{-1}, strongly suggestion the existence of diclofenac sodium in the products.

X-ray diffraction patterns of the obtained microtablets had shown that the drug present was in crystalline form. Although, the intensity of X-ray diffraction peak of product was weaker than that of pure diclofenac sodium, most characteristic peak of diclofenac sodium were detected. The microtablets with HPMC and with EC exhibited major diffraction peaks, but intensities of DS peaks was reduced indicated that some crystals in the product might convert to a disordered forms. It was possibly due to mixing and compression processes of microtablets. Moreover, DS in the microtablets showed less peak intensities because there were large amount of additive that compound with DS. Hence, interfering of other additives may decrease intensity of DS peaks (Betageri et al., 1996). There were some new peaks in the X-ray diffraction patterns of microtablets. This was due to some peaks of other additives, such as lactose at the diffraction angles of 18.92, 19.43, 19.97 and magnesium stearate at the diffraction angles of 5.44, 21.92.

DSC analysis could be used as a quick screening tool for preformulation studies to study the potential incompatibilities of ingredients in the solid state (Fassihi, 1985). From thermograms of the microtablets, every formulation did not show major peaks of diclofenac sodium whereas minor peaks were detected. These minor peaks might be the peaks of components in formulations. The DSC duplication results still could not detect the existence of diclofenac sodium in the obtained microtabets whereas the X-ray diffraction peak and IR spectra exhibited major peaks of diclofenac sodium. This was perhaps due to heat labile of diclofenac sodium in this method. In addition, equipment and method of detection may affect to detection the peak of diclofenac sodium.

There were several reports about disadvantages of differential scanning calorimetry (DSC). Suryanarayanan et al. (1997) found that it was almost impossible to measure the enthalpy of dehydration by conventional differential scanning calorimetry whereas the pressure differential scanning calorimetry could measure clearly. Yonemochi et al. (1997)

found that differential scanning calorimetry and X-ray diffraction could not measure the difference of two amorphous states of ursodeoxycholic acid whereas isothermal microcalorimetry could measure it.

Differential scanning calorimetry (DSC) results were reported to be not correlated to other methods. Carstensen et al. (1995) studied and distinguished polymorphic forms of N-[2-{{{-5-{(Dimethylamino)methyl}}-2-furanyl]thio]ethyl-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride. They found that two polymorphic were not distinguished by DSC and solubility. Only X-ray diffraction was possible to detect. William (1994) found that the ability to detect forms I and II of stanozolol and mixtures of these crystal forms was shown to be very difficult with differential scanning calorimetry due to the ability of form II to transform to form I. When transformation occurred prior to melting, there was a tendency to misinterpreted DSC data. Whereas the X-ray diffraction and Fourier transform infrared spectroscopy could analyze and resolve patterns of each form.

Therefore, the other methods, such as Isothermal microcalorimetry, NMR should be tested to clearly support the DSC results. However, they are not investigated in this study.

Conclusions

Diclofenac sodium sustained release microtablets could be prepared by conventional tablet production method of wet granulation with an appropriate amount of cellulose derivatives. There were two factors, type and amount of cellulose derivatives, that found to affect the physical properties of granules and microtablets. Most physical properties were unsatisfactory such as poor flowability, low hardness and high friability when the amount of HPMC and EC was increased. The EC formulations showed that the physical properties of granules and microtablets were better than that of HPMC formulations. In addition, the type and amount of cellulose derivatives affected drug release rate. Dissolution studies revealed that using ethylcellulose could achieve the effective controlled release system. These EC microtablets gave amount of drug release in 24 hours about 94.10% and 89.19% at low EC content and high EC content, respectively. Their percentage of drug release passed the specification in USP XXIV but their drug release patterns were different form the pattern of Voltaren SR 75 mg. The slopes of the pattern of EC microtablets deivided as a concave

curve in the first time intervals and as a straight line at a constant drug release whereas the slope of Voltaren SR 75 mg was a straight line. Moreover, the drug release of EC microtablets was faster than that of Voltaren SR 75 mg at the same time. On contrary, HPMC microtablets could not achieve the effective controlled release system. Their percentages of drug release of low HPMC content and high HPMC content microtablets were 66.26% and 60.72%, respectively that did not pass the specification official standard USO XXIV. However, the drugs release patterns were similarly to Voltaren SR 75 mg. The microtablets of low HPMC content showed the drug release pattern was more similar than those of high HPMC content. Therefore, the selection of capsule size used for modifying drug release patterns of HPMC formulations to be same as that of Voltaren SR 75 mg. It was found that the suitable was capsule size NO. 1. The proper formulation used HPMC at low content to produce diclofenac sustained release microtablets that filled into capsule NO. 1. This microtablets gave amount of drug release about 75.84 % in 24 hours, the model of drug release was first order model.