CHAPTER IV

Discussion and Conclusion

In the process of preparing prolonged action dosage form, each step or ingredient is important in itself to the release of the drug from dosage form which in this experiment, is compressed matrix tablet, for example, mixing retarding agent within prepared granules, physicochemical properties of active ingredients, the utilization of other excipients, the availability of the retarding agents, types of granulating liquid, shape of the compressed tablet especially its diameter and thickness, and the compressional force given to tablet.

In the preparing of aspirin sustained release tablet, aspirin 650 mg was chosen to be the dose in this formulation. The criteria to select other ingredients and appropiate procedure were to avoid incompatability problems with aspirin which is a relatively strong acid and easily to be hydrolysed, and to produce a sustained release dosage form. The following ingredients were used to the study of the above criteria.

Polyvinylpyrrolidone (P.V.P. K-30)

P.V.P. K-30 was used as the binder in aspirin sustained release tablet. It is already known that water cannot be used as the granulating solvent in aspirin formulation because aspirin is unstable and hydrolysed in the presence of water. The appropriate granulating solvents for the sustained release aspirin are organic solvents such as alcohol, chloroform etc. P.V.P. K-30 was used as the binder in this formulation because it could dissolve in organic solvent. P.V.P. K-30 makes wet granulation of

the water sensitive ingredients possible in an organic solvent so that the stability of each component is satisfactorily maintained. P.V.P. stabilizes aspirin. Studied on aspirin tablets granulated with it showed no free salicylic acid after one month at 40°C, or three months at room temperature, with only slight loss of potency (52).

The concentration of P.V.P. as the binder in the formulations were 1%, 3%, 5%, 7% and 10% w/w of aspirin (Table 5). Considerable interest has been developed in studying the suitable content of P.V.P. that would provide good granules for tableting. Tables 16-20 show the study of dissolution rate of aspirin tablets which contain various contents of P.V.P. in the formulations. At every concentration of P.V.P. (Figure 19), the dissolution rate was essentially the same, increasing the amount of P.V.P. did not affect the dissolution of aspirin. From the experiment, 5% P.V.P. provided good granules for tableting than other concentrations. The concentration of P.V.P. that less than 5% w/w gave too much fine granules and caused problems in tableting because a higher compression force was required to produce desired hardness, On the otherhand, concentration of P.V.P. more than 5% w/w also caused difficulty in screening the damp mass of aspirin into granules, for the damp mass was sticked at the pores of the sieve. Therefore the suitable concentration of binder for the sustained release aspirin formulation was 5% P.V.P..

Absolute alcohol

Aspirin, a heat sensitive drug, was granulated in absolute alcohol and dried at low temperature (37°C) for 3 hours. It was nescessary to prevent degradation of aspirin, so absolute alcohol was used as the granulating agent since it is volatile solvent. Drying

at low temperature within short period of time by this solvent is possible.

Stearic acid

Aspirin is considered to be a relatively stronge acid. It is incompatible with alkaline lubricants. Alkaline stearate such as; magnesium stearate, calcium stearate, aluminium stearate accelerated hydrolysis of aspirin (53, 54, 55). Kornblum and Zoglio indicated stearic acid to be suitable lubricant for used in aspirin tablet (53). The experiment used content of stearic acid; 0.25%, 0.5%, 1.0%, 1.5%, 2.0%, 2.5%, and 3.0% w/w of granules, and to be considerably suitable content that provided good apparent tablet. The experiment was performed and found that stearic acid 2,5% w/w of granules was suitable concentration for sustained release aspirin formulation. Adding stearic acid less than 2.5% w/w of granules gave sticky problem at the surface of the punch. The sticky problem was not found at 2.5% and 3.0% stearic acid as well, but consider on the costing of tablet , the concentration at 2.5% stearic acid was selected.

Silinium tetrachloride (Aerosil 200)

Aerosil 200 was used as a glidant of granules so the granules flow uniformly into a punch and die, and the granules were compressed to achieve constant weight of tablet during compression. The amounts of Aerosil 200 were varied to be 0.1%, 0.25%, 0.5%, 0.75% and 1.0% w/w of granules . The evaluation indicates that Aerosil 200 0.5% w/w of granules provided constant weight of tablet. The concentration of Aerosil 200 less than 0.5% of granules showed unsmoothly-flow of granules. The concentration more than 0.5% Aerosil 200 also

the granules flowed uniformly but for economical reason, Aerosil 200 0.5% was chosen.

In addition to the criteria to select appropiate ingredients, the process of preparing aspirin sustained release formulation was also important. The granules was prepared by wet granulation method and drying at 37°C for 3 hours. The drying temperature of normal condition for drying process is between 50-60°C, but in this research the chosen temperature was 37°C in order to prevent the degradation of aspirin. The hydrolysis of aspirin is very sensitive to temperature changes. The decomposition rate of aspirin (50-100 mesh) at 37°C over a storage period of six months at 84% relative humidity was only 0.21% (56).

The size and shape of punch and die are also important to the convenient for patient to regiment. Because of high dose of aspirin, the flat-faced beveled edge puch which having a diameter of 14 mm were used.

The thickness of tablet was also included to be considered. Eventhough some reports showed that compressional force and compressional period did not significantly affect dissolution rate of tablet. Nakano et al (57) studied sustained release of theophylline from hydroxypropylcellulose tablet, they indicated that compressional force and compressional period were not important factors in modifying the release pattern of the drug. However, some publications reported that compressional force significantly affected dissolution rate of sustained release tablet. Wiseman and Federici (13) studied the experimental restaining matrices of aspirin sustained release tablet,the

rate of aspirin release was found to be controlled by the hardness to which the tablet was compressed. For example, tablet which had hardness of 10.6 kg exhibited no sustained action, but of hardness of 11.5 kg exhibited good sustained properties.

In this investigation, when the hardness of tablet was about 9-10 K.P., aspirin tablet could not restrain its intact shape and disintegrated before the desired time (less than 2 hours). This cause problems in dissolution mechanism of drug from matrix form. In sustained action of compressed matrix, drug will be gradually dissolved and diffused from restrained-matrix. According to the preformulation it was found that increasing hardness of aspirin tablet, increased disintegration time. The hardness of 13-15 K.P. gave disintegration of more than 3 hours. This hardness was used for the whole experiment. Hardness more than 15 K.P. would cause damage to the tablet machine. The average hardness of prepared formulations was about 14 K.P. (Table 11).

Table 19 shows the effect of concentration of P.V.P. on dissolution rate of aspirin in various time interval. At any time interval, the dissolution rates of aspirin from tablets containing different concentration of P.V.P. were not significantly different. According to Kulvanich's experiment, he found that increasing the amount of P.V.P. did not affect dissolution rate (58).

Figures 20,21,22 and 23 demonstrate the release patterns of aspirin from the tablets containing the same amount of the drug but difference amounts of Methocel A-15LV, Methocel A-4C, Methocel A-15C and Methocel A-4M respectively. The drug was released from tablet

more slowly with an increasing in Methocel A contents therefore the release rate of the drug could be modified by changing the Methocel A contents in the tablets. Huber, Dale and christenson (23) studied the influence of hydrophilic gums on dissolution behavior of control release tablet. The percentage of hydrophilic gums in the formulation had a marked influence on the dissolution behavior of the tablet.

Figures 24, 25 and 26 show the release patterns of aspirin from tablets containing different grades of Methocel A at the amount of 5%, 10% and 15% Methocel A respectively. The release rate of aspirin from the tablets containing the low molecular weight of Methocel A-15LV was faster than the release rate from tablets containing the polymer of medium and high molecular weight grades, Methocel A-4C and Methocel A-4M. But the release rate from tablet containing Methocel A-15C was the slowest. At every concentration of Methocel A, the release rate of aspirin was conversely to the degree of polymerization of Methocel A except Methocel A-15C which molecular weight is less than Methocel A-4M but the release rate of Methocel A-15C was shower than Methocel A-4M. It is possible that a certain grade and viscosity of Methocel A may be suitable to the formulation so the porosity is reduced and the tortuosity is increased.

Various grades of Methocel A used in this research are hydrophilic matrices which can be classified as water soluble polymer. The velocity of penetration (S) of solvent into bulk polymer can be described as (5).

$$S = kM^{-A} \qquad (\text{eq. } \underline{n} \text{ 5})$$

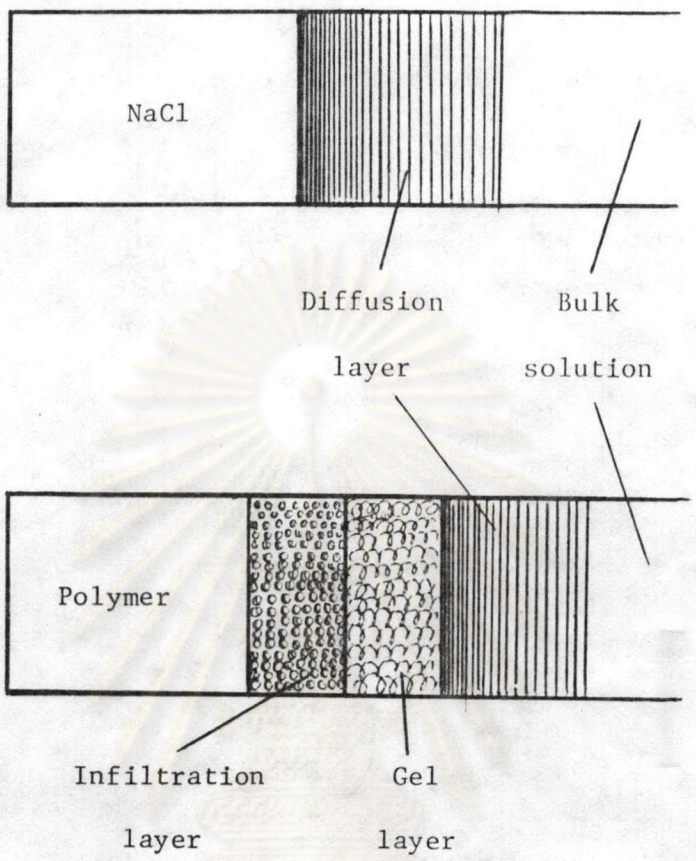

Figure 27 : Penetration of solvent into polymer and soluble crystalline material compared (5).

S = velocity of penetration

M = molecular weight of polymer

k, A = constant

P.V.P. can be classified as the polar polymer and the release mechanism from P.V.P. is dissolution controlled process (5).

Figures 20-26 show the percentage release of drug in various period of time from sustained release dosage form. The graph profiles can be divided according to the percentage release of drug into 4 intervals which are

In simulated gastric fluid ;

Interval 1, period of time 0-30 minutes

Interval 2, period of time 30-180 minutes

In simulated intestinal fluid ;

Interval 3, period of time 180-360 minutes

Interval 4, period of time 360-480 minutes

Tables 21-32 show the percentage release of aspirin per hour in various period of time. In the first interval (0-30 minutes), it was seen that the release rate of aspirin was higher than the second interval (30-180 minutes). Since in the first interval, rate determining step of aspirin release mainly controlled by dissolution rate of P.V.P.. Methocel A needs a period of time to form gel so in this interval diffusion mechanism from Methocel A shows a little effect. Due to this result, aspirin did not have to diffuse through gel layers of Methocel A, the percentage release of aspirin in first interval was more than other intervals. This effect can be clearly seen in the fifth minute which had the percentage release

higher than other intervals of time especially in control formulation (with out Methocel A). However the release rate from control formulation of the fifth minute was 24 % per hour and higher than the formulations containing Methocel A. The difference of the percentage release was also clearly seen when compared control formulation with formulation containing 15 % Methocel A-15C. From the latter formulation, aspirin release rate in the fifth minute equaled tO 10.5 % per hour. This result may come from the occuring of the clean surface at the surface area of tablet by compression force during tableting and lubricant property used in the formulation which was stearic acid The fraction of aspirin in the surface area would rupture due to compressional force and caused some amount of aspirin at the clean surface free from coated polymer, therefore the release rate of aspirin was high. Contrary the formulation that contained Methocel A, the polymer would surround to the part of aspirin that rupture from the granules of surface area of tablet. In simulated gastric fluid, Methocel A would swell and formed infiltration and gel layers respectively as shown in Figure 27. Aspirin had to diffuse through these layers before reaching bulk solution. This mechanism caused in decreasing the release rate of aspirin.

In the second interval (30-180 minutes) from graph profiles (Figures 20-26), the effect of clean surface was then deminished and it was found that the percentage release rate began to be constant (Tables 21-32). The mechanism of aspirin release from tablet could be described by two mechanisms, the diffusion mechanism (equation 3) which was the effect from Methocel A and the dissolution mechanism from P.V.P. .

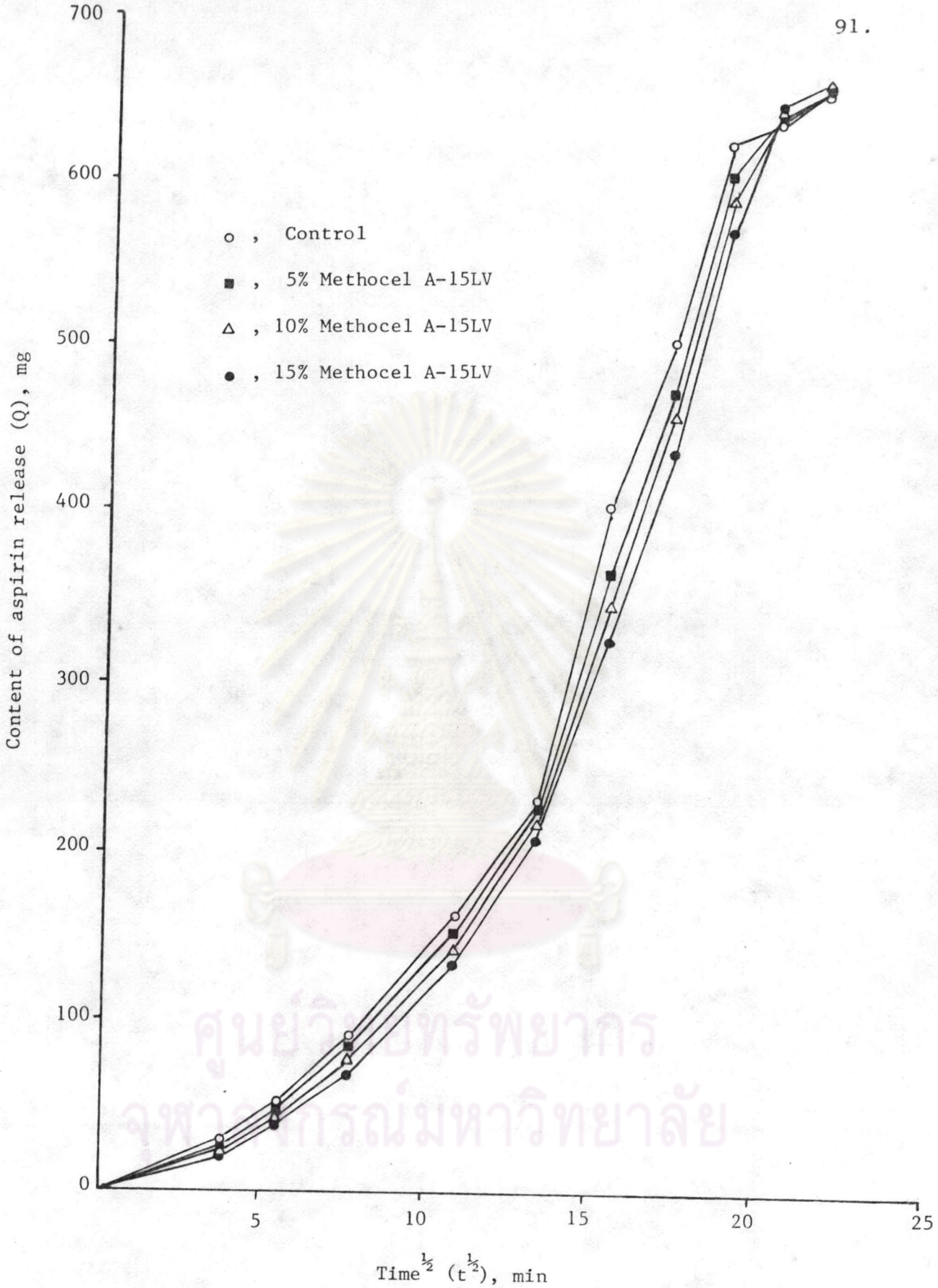

Figure 28 : Relationship between the content of aspirin release (Q) and the square root of time ($t^{1/2}$) from aspirin tablets contain various concentrations of Methocel A-15LV.

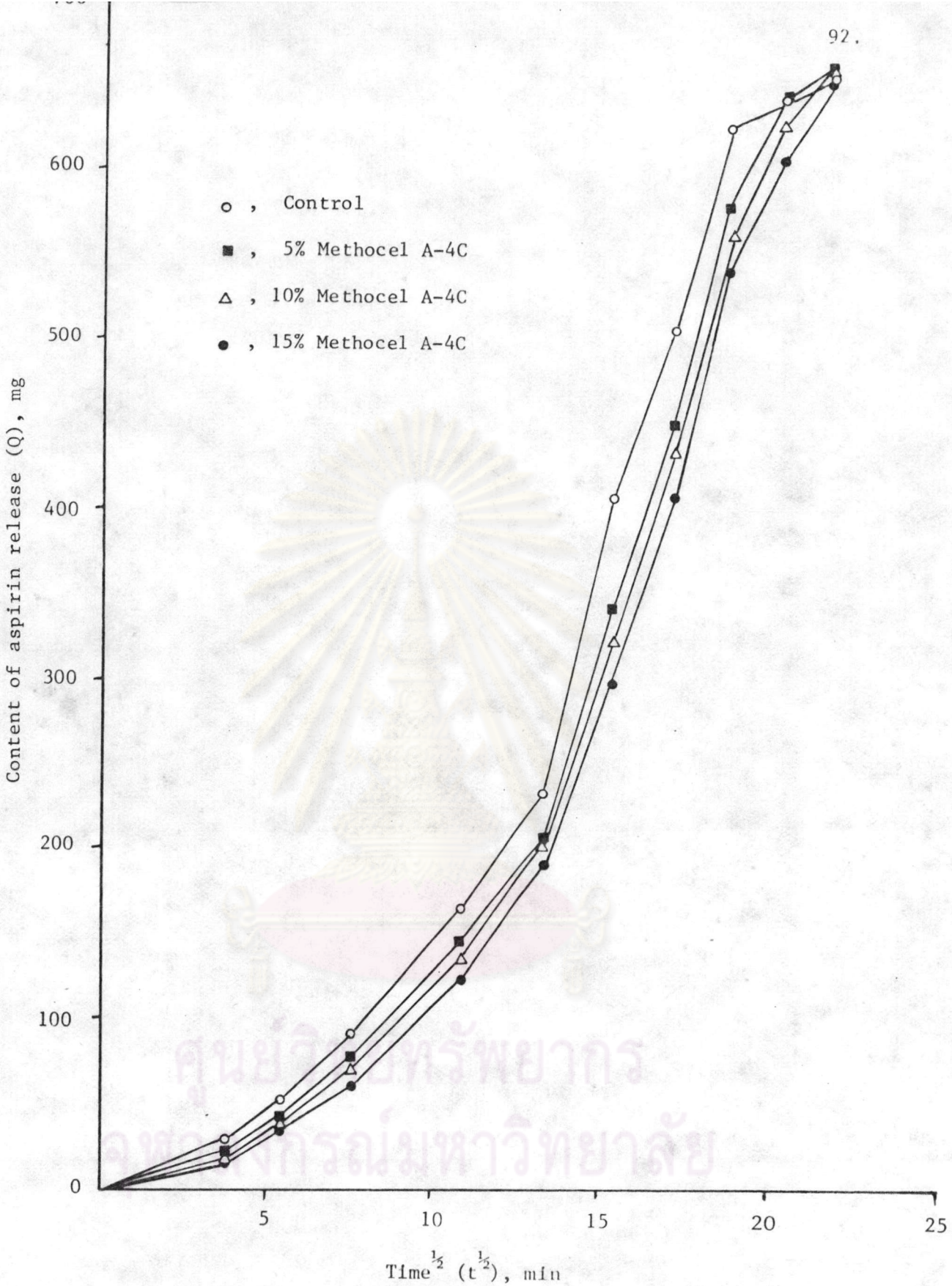

Figure 29 : Relationship between the content of aspirin release (Q) and the square root of time ($t^{\frac{1}{2}}$) from aspirin tablets contain various concentrations of Methocel A-4C.

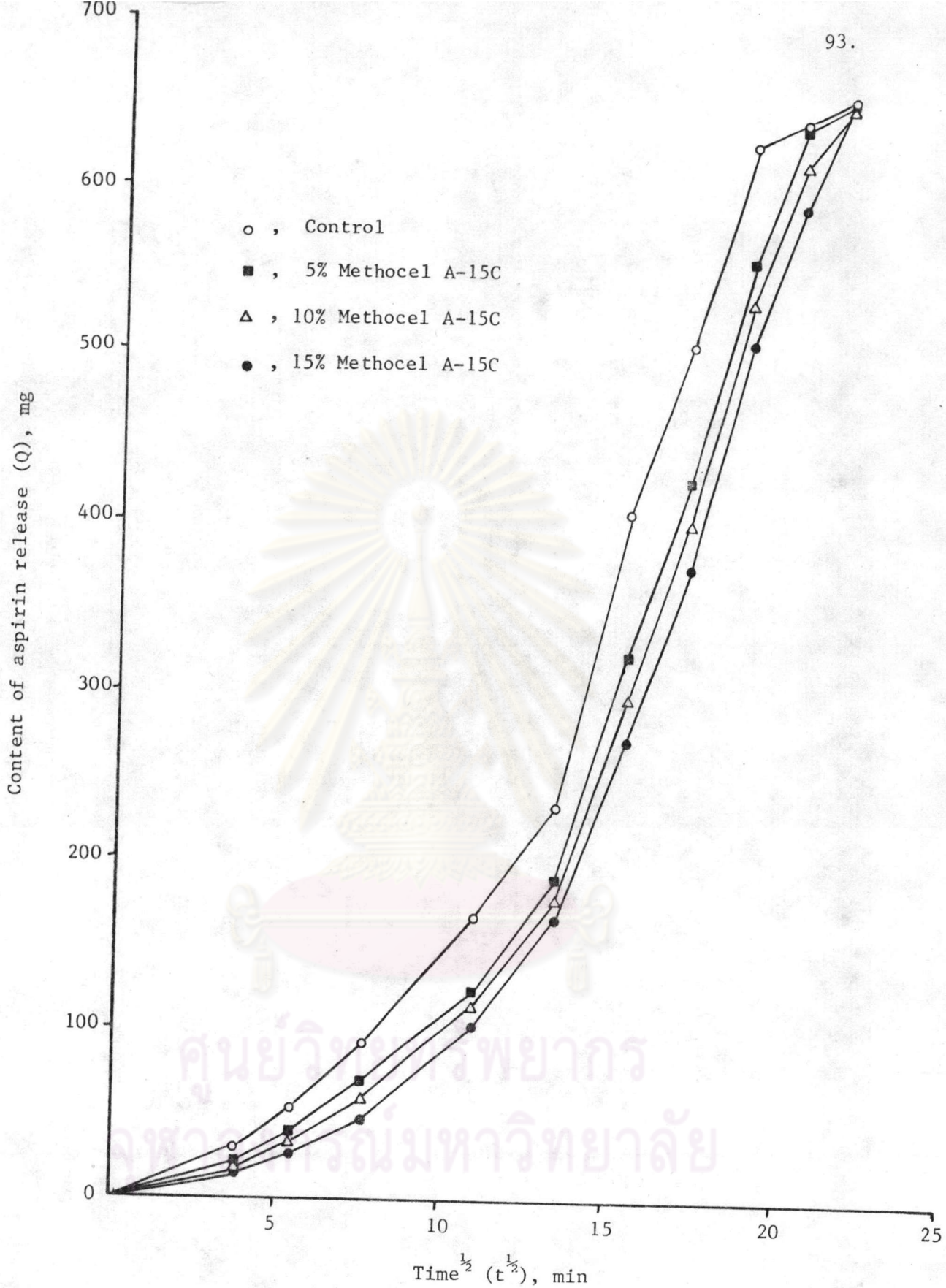

Figure 30 : Relationship between the content of aspirin release (Q) and the square root of time ($t^{\frac{1}{2}}$) from aspirin tablets contain various concentrations of Methocel A-15C.

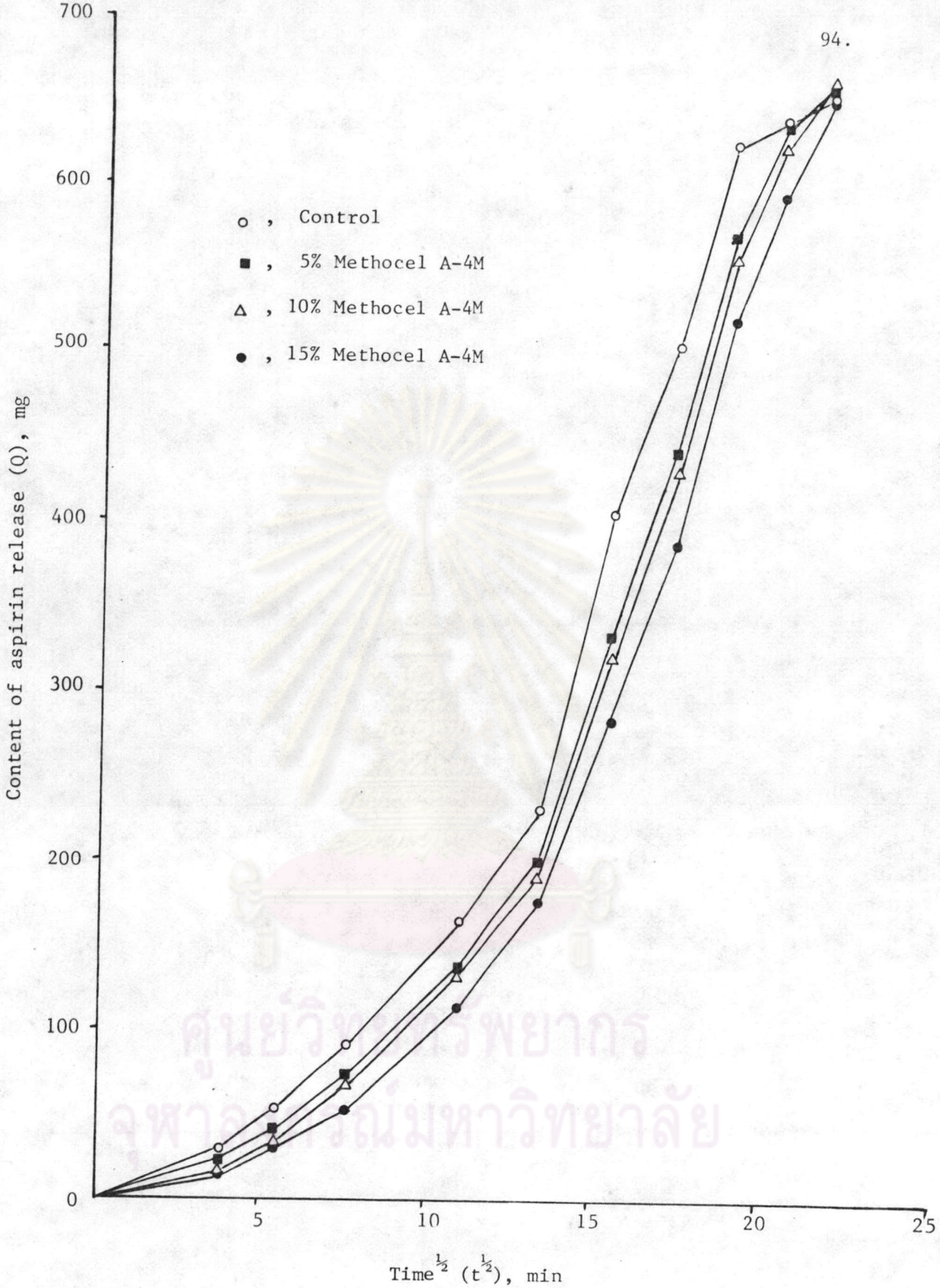

Figure 31 : Relationship between the content of aspirin release (Q) and the square root of time ($t^{\frac{1}{2}}$) from aspirin tablets contain various concentrations of Methocel A-4M.

$$Q = kt^{\frac{1}{2}} \qquad (\text{eq } \underline{n} \ 3)$$

Q = content of drug release

t = the dissolution time

k = constant

The graph profiles of Q vs $t^{\frac{1}{2}}$ were shown in Figures 28-31. In period of time 180-360 minutes, graph profiles of Q vs $t^{\frac{1}{2}}$ reveal a linear relationship which indicated that the mechanism of release was diffusion controlled process. In 30-180 minutes, the release rate of aspirin showed a deviation from the linear relationship because the controlled process at this period of time was dependent on both diffusion and dissolution mechanisms. It is common to see both diffusion and dissolution mechanisms operate in a given dosage form, however one mechanism will usually predominate over the other.

In the step of preparing aspirin granule, aspirin and Methocel A were enclosed by P.V.P. - K30 into granule so at the begining of release drug into simulated gastric fluid, the release rate of aspirin would depend on the dissolution rate of P.V.P.. In the following period when simulated gastric fluid could tough Methocel A and caused Methocel A to swell (Figure 27), this period, rate of release aspirin would depend on the velocity of penetration (S) of solvent (simulated gastric fluid) into the bulk polymer as shown in equation 5.

$$S = kM^{-A}$$

S depends on molecular weight of polymer.

Aspirin at the surface area of tablet would diffuse through infiltration and gel layers of polymer into simulated gastric fluid. Rate determining step of release drug from matrix was diffusion of

aspirin which passed in opposit direction of simulated gastric fluid gradient across the diffusion layers. Therefore, there were many factors that controlled the release rate of drug from the tablet. These factors were the velocity of dissolution rate of P.V.P., the velocity of swelling of Methocel A and the rate of diffusion of aspirin through gel layers of Methocel A.

Since the process of preparing matrix gave the gel layers of Methocel A, occured by swellen of polymer when contacted with simulated gastric fluid became uncontinuous layers rather than continuous layers liked as when adding rate retarding agent outside the granules. So rate of swelling of Methocel A rely on dissolution rate of P.V.P. Each profile of releasing rate of every formulations depend on the dissolution mechanism of P.V.P. This point was very interest since it had known well that adding only one type of retarding agent into formulation could not present the property of ideal retarding agent. Adding Methocel A in this preparation acted like regulator and the release drug from matrix could be controlled to release a disired.

In simulated intestinal fluid, the mechanism of release drug was diffusion controlled mechanism of Methocel A. The graph profiles between Q vs $t^{\frac{1}{2}}$ (Figures 28-31) gave straight line rather than in simulated gastric fluid, This may be that in this period of time, the most fraction of P.V.P. was dissolved, so Methocel A acted as controller in this releasing,

When observe the graph profiles of every formulations it found that the slope of releasing in simulated gastric fluid was lower than that in simulated intestinal fluid in every formulations of experiment. This is due to two factors which were the effect of physicochemical

properties of aspirin and Methocel A. The ability to dissolve of aspirin in simulated gastric fluid and in simulated intestinal fluid was different, that was, in acid solution of simulated gastric fluid (pH 1.2) the solubility of aspirin is less than in alkaline solution of simulated intestinal fluid (pH 7.5)

Oweing to the acidity of aspirin, rate of dissolution was depend on pH of medium and could express by the equation 6 (10).

$$pHp = pKa + \log_{10} \frac{Cs - So}{So} \quad (eq\ \frac{n}{}\ 6)$$

pHp = pH at which the weak acid will just begin to precipitate out of solution

pKa = negative $\log_{10}$ of the dissociation constant

Cs = the molar concentration of the salt species

So = the molar concentration of the weak acid species in aqueous solution

In addition to the above factors, the pH also affected Methocel A by causing the viscosity of Methocel A decreased. At pH below than 3, the ability of hydration of ether lingkage would decrease because of reducing in protonation process.

The pH of simulated gastric fluid in this investigate was 1.2, therefore this pH could affect to the hydration of Methocel A polymer and resulted in decreasing its viscosity. These affecting factors did not occur in simulated intestinal fluid which had a pH of 7.5.

The reduction in viscosity of polymer brought about increasing the release of aspirin from Methocel A- polymer. But when compared the affect factors between physicochemical properties of aspirin had

more influence than the decreasing hydration of Methocel A.

In the fourth period (360-480 minutes) the slopes of graph profiles were lower than those in the third period (180-360 minutes), this resulted from the erosion in some parts of swollen Methocel A and caused the rate of release aspirin to decrease as well.

It is noticeable that the release rate at 480 minutes was the lowest because total amount of aspirin was mostly dissolved before 420 minutes. Therefore the release mechanism in this fourth period was resulted from diffusion mechanism as well as erosion of Methocel A.

Conclusious

This investigation was to prepare sustained release aspirin tablet which had sustained action over 8 hours. Methylcellulose (Methocel A) was used as the rate retarding agent and the matrix dosage form was selected in this study. The results of preliminary study was hoped to be useful and applicable to product developement of sustained release aspirin tablet.

On the basis of the experimental results it may be concluded as the following :

P.V.P. K-30 used as the binder in aspirin sustained release tablet, showed dissolution-retarding property. Increasing the amount of P.V.P. K-30 did not significantly affect the dissolution of aspirin.

Increasing concentration of various grades of Methocel A decreased the dissolution of aspirin. And increasing the degree of polymerization of Methocel A also decreased the dissolution of aspirin except of Methocel A-15C. It could be seen that Methocel A-15C was

considered to be appropiate to use as a retarding agent because it retarded the release of aspirin more than the other grades. For the formulations in the experiment, it was found that formulation # 12 in which 5% Methocel A-15C was used as a retarding agent,was the best formulation because the release of aspirin from the matrix is considerable slower than control formulation. Eventhough the release aspirin in this formulation was more than that in formulation containing 10% Methocel A-15C or 15% Methocel A-15C, the ability of higher concentration of Methocel A-15C used in formulation to decrease the release rate was not encouraged. It was concluded that formulation containing 5% Methocel A-15C was the best formulation in this experiment.

The predominant mechanism of the release rate of aspirin from matrix dosage form in simulated gastric fluid is dissolution controlled mechanism. This mechanism is related to physicochemical property of aspirin, Methocel A and dissolution of P.V.P. - K30. In simulated intestinal fluid, the predominant mechanism is diffusion controlled mechanism which relate to the swelling property of Methocel A.

This research provided the empirical idea to use a suitable polymer to form a sustained release aspirin formulation as matrix dosage form in desired time. The result from this research clearly showed that although individual polymer would usually predominant over the other, but using only one types of polymer could not reach the perfect property to give constant release rate of drug from the tablet.