CHAPTER I

INTRODUCTION

General to be accepted that a drug to be available to the body, it must to be in solution and the dissolution of the drug from a formulation may affect both its absorption and therapeutic characteristic. The drug must be in dissolved state before being absorbed into blood circulation as shown in figure 1[1]. For most tablets, the first important step in the sequence is the breakdown of tablet into smaller particles or granules. This process is known as disintegration.

Figure 1 indicates that when a tablet is exposed to dissolution fluid, the dissolution of a drug occurs not only from a fine particles of the drug but also from an intact dosage form before its disintegration and from fragments and agglomerates produced after disintegration. It is concluded that the dissolution rate of a drug can be a rate-determining step in the absorption process. Thus, for poorly soluble drugs, the dissolution has greater effect on absorption rate of the drug.

Since a drug must normally be in solution before absorption can take place, orally administered tablets must have their drug dissolved in the contents of the gastrointestinal tract before the absorption can occur. However it is obvious that a correlation exists and obvious consequences of data of disintegration time and dissolution halftime

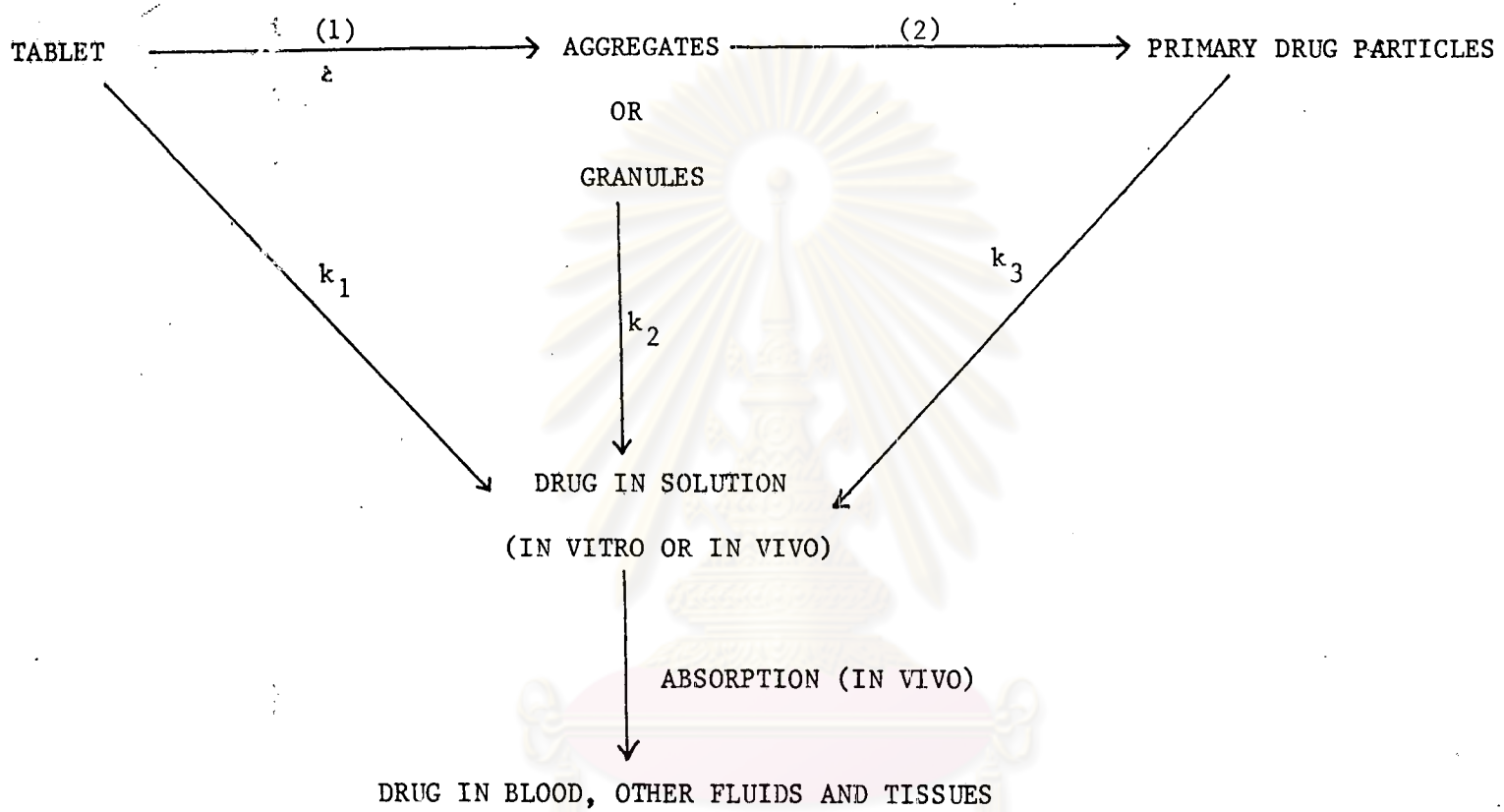

Figure 1 Drug dissolution from a tablet dosage form followed by absorption into the bloodstream.

(1) = Primary disintegration step. (disintegration) (2) = Secondary disintegration step. (deaggregation) ; k_1, k_2, and k_3 = Dissolution Rate constant from tablet, granules, and primary particles, respectively.

are attempted to ameliorate the dissolution by improving disintegration [2].

Increasing dissolution rates of pharmaceutical systems containing digoxin by using polyvinylpolypyrrolidone as a tablet disintegrant showed that it was possible to produce digoxin tablets with a bioavailability of 82 % . These tablets reached the same high level in bioavailability as an aqueous/alcohol digoxin solution[3]. Therefore, a rapid disintegration process is prerequisite for a good bioavailability. It was generally recognized that disintegration time would be decreased as the disintegrant concentration was increased[4,5,6]. However an opposite result was reported the disintegration time could be increased with increasing disintegrant concentration[7]. A rapid disintegration of tablet did not ensure a rapid dissolution rate of the drug, since the discrete particle may be covered with additives. The dissolution of a drug from tablet is affected by many factors which have been reported by several investigators[8]. Nevertheless, dissolution test is useful and valid, as a quality control procedure, in product development, in the detection of lot to lot variation, and comparison the different products from various manufacturers. Therefore, since 1970, The United States Pharmacopoiea and The National Formulary have provided procedures for dissolution testing to meet requirement as specified in individual monograph[9, 10].

Dissolution Theory

1. The theory of dissolution, presented by Higuchi[11], states that there are three processes which either alone or in combination describe dissolution rate mechanism : The diffusion layer model, the interfacial barrier model, and Danckwert's model, as shown

in figure 2.

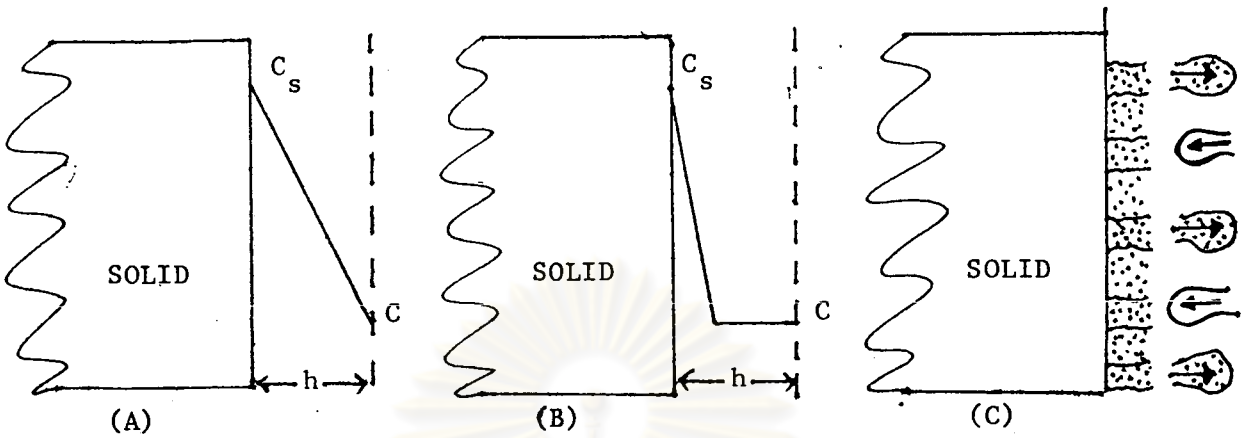

Figure 2 Mechanism of dissolution : (A) Diffusion layer model, (B) interfacial barrier model, (C) Danckwert's model[12]

Dissolution by the diffusion layer model is diffusion-limited and consists of two stages : (1) interaction between the solvent with the surface of the drug, resulting in the hydration and solution of the drug to form a layer saturated solution arround the drug particle, (2) the diffusion of the drug molecule into the bulk system. The diffusion of the drug away from the saturated layer is regarded as the rate determining step.

For interfacial barrier model, it is proposed that all collision of solvent molecules with solid surface do not result in release of solute molecules because of high free energy of activation requirement.

Danckwert's model postulates that removal of solute from the solid is achieved by macroscopic packets of solvent being carried right up to the solid-liquid interface by eddy current.

Noyes and Whitney[13] proposed that the relationship under standard condition of agitation and temperature for dissolution rate of solid was

$$\frac{dw}{dt} = k\, s\, (C_s - C_t) \qquad \text{.....(1)}$$

where k = dissolution rate constant

$\frac{dw}{dt}$ = the loss of weight of particle per unit time.

s = surface area of solid

C_s = concentration at saturation

C_t = concentration of the solid at a given time. When C_t is less than 15 % of saturation solubility, C_s, C_t is negligible. Under sink condition,

$$\frac{dw}{dt} = ksC_s \qquad \text{.....(2)}$$

2. Hixon and Crowell's Cube-Root Equation[13] postulates that when solid dissolves, the surface area changes with the time. Crowell Cube-root equation for dissolution is based on assumption that :

(1) Dissolution occurs normal to the surface of the solute particle.

(2) Agitation is uniform overall exposed surface and there is no stagnation.

(3) The particle of solute retains its geometric shape.

For monodisperse powder with spherical particles of radius "r", the surface area "s" of N particles at the time "t" is

$$s = N \times 4\pi r^2 \qquad \text{.....(3)}$$

The change in volume of the particle or the volume of particle dissolved over infinitesimally small time increment, dt, is

$$dV = -N \times 4\pi r^2 dr \quad \text{.....} (4)$$

since $\frac{dw}{dt} = ksC_s$; and ρ = density of particle

$$dw = \rho dV = ksC_s dt \quad \text{.....} (5)$$

$$-\rho N \times 4\pi r^2 \frac{dr}{dt} = k \times N \times 4\pi r^2 C_s$$

$$-\rho \frac{dr}{dt} = kC_s \quad \text{.....} (6)$$

$$r = r_o - \frac{kC_s t}{\rho} \quad \text{.....} (7)$$

$$d = d_o - \frac{2kC_s t}{\rho} \quad \text{.....} (8)$$

where "d" is the diameter of particle and "d_o" is the diameter at t=0.

The weight of spherical particle (w) is related to its diameter (d),

$$w = N\rho \frac{\pi}{6} d^3 \quad \text{.....} (9)$$

$$w^{\frac{1}{3}} = (N\rho \tfrac{\pi}{6})^{\frac{1}{3}} d$$

$$w_o^{\frac{1}{3}} - w^{\frac{1}{3}} = Kt \quad \text{.....} (10)$$

where $K = w_o^{\frac{1}{3}} \left(\frac{2kCs}{\rho d_o}\right)$ .....(11)

K is the cube-root dissolution-rate constant.

3. Dissolution of Direct-Compressed Tablets.

$$w_o^{\frac{1}{3}} - w^{\frac{1}{3}} = K(t-t_1) \quad \text{.....} (12)$$

when t_1 is disintegration time

$$K = w_o^{\frac{1}{3}} \frac{2kCs}{\rho d_o}$$

$$k = \frac{D}{h} = K \frac{\rho d_o}{2C_s w_o^{\frac{1}{3}}} \text{ cm sec}^{-1}$$

where D = diffusion coefficent

h = thickness of liquid film

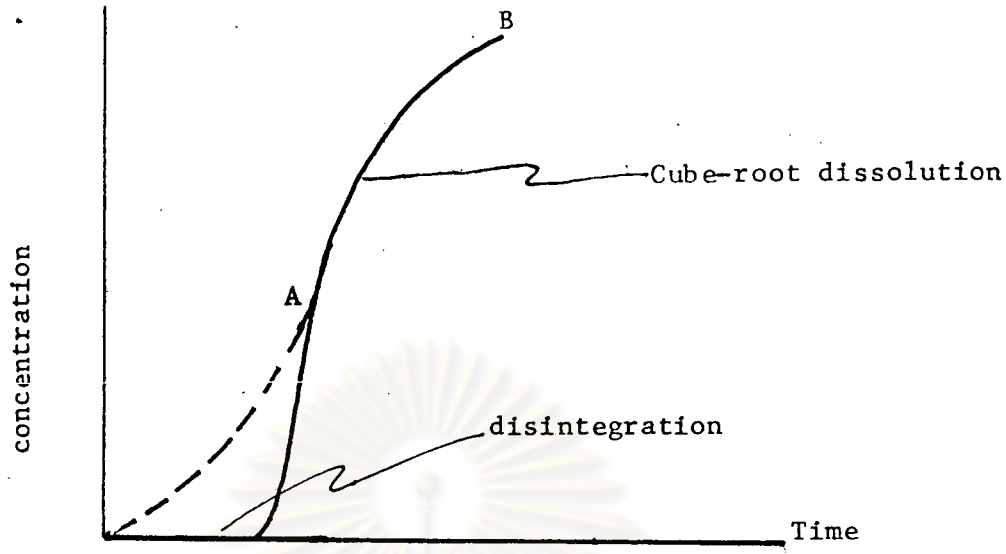

Figure 3 Dissolution-rate curve for a directly compressed or slugged tablet (14)

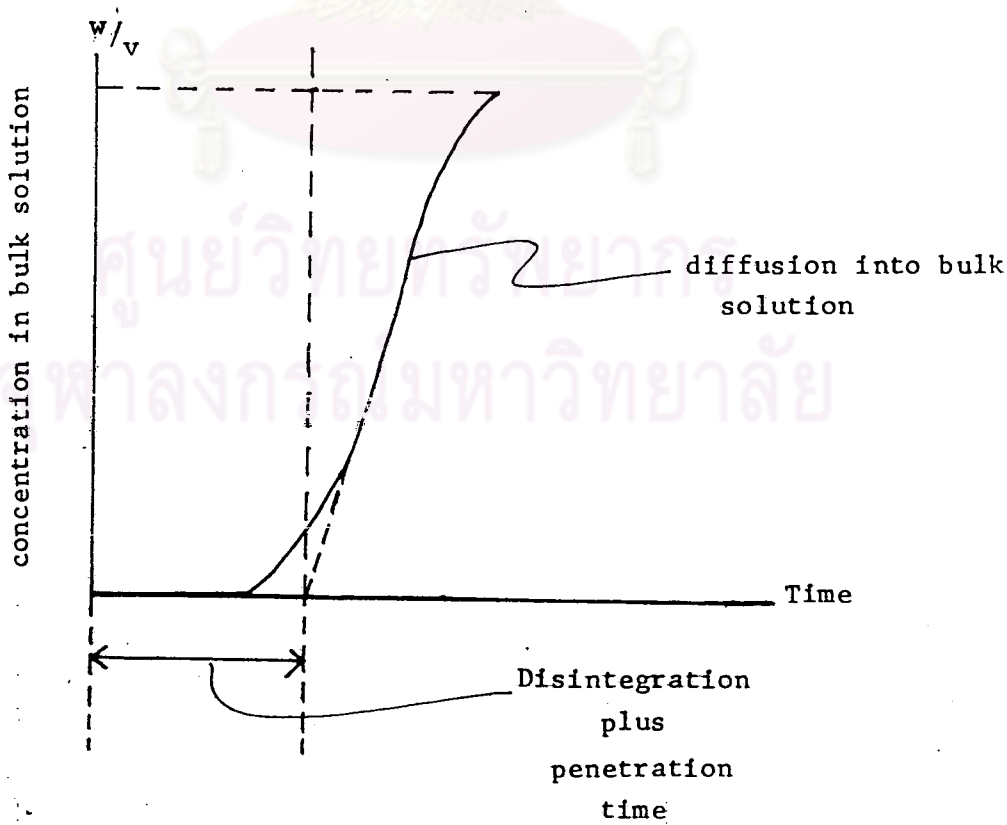

Figure 4 Dissolution-rate curve for a wet granulated tablet (14).

4. Dissolution of Wet Granulated Tablets.

When tablets are manufactured by wet granulation technique two cases may be considered.

First, for the disintegration of tablets into porous granules and diffusion of drug from the granules into bulk solution.

$$\ln(\frac{W}{V} - C) = -k' (t-t_1-t_2) + \ln \frac{W}{V} \quad \text{.....(13)}$$

where k' = dissolution rate constant
v = volume of bulk solution
W = the amount of drug in dose being dissolved
C = the concentration of drug in the solution
t = time, t_1 = the disintegration time of tablet into granules, t_2 = the time required for penetration of liquid into porous granules.
$(t-t_1-t_2)$ = the time for the drug to diffuse into bulk solution

The second case, the granules contain insoluble material and are relatively non porous, the time for penetration of the liquid into granules may be rate determining rather than the process of drug diffusion into bulk solution. In this case the drug is released from the granules according to the equation:

$$Q = (K' \beta \epsilon t)^{\frac{1}{2}} \quad \text{.....(14)}$$

where Q = the amount of drug dissolved per unit area of surface
β = the fraction of drug in the tablet or granule
ϵ = the porosity of the granules or dosage form mass.
t = the time
K' = a constant equals to $2DC_s$, where "D" is the

diffusion coefficient of drug in dissolving medium, and "C_s" the solubility of drug in medium[15].

Preparations in solid oral dosage forms containing poorly soluble drugs always have problems in solubilization of these drug in the gastrointestinal fluid. The rates of absorption of the drugs from the stomach or intestinal are limited. Thus, the bioavailability are incomplete. Several methods have been approached to overcome these problems.

A marked increase of dissolution rates and attainment of supersaturation of griseofulvin, were found by Chiou and Reigelman[16]. They dispersed the drug in the matrices of polyethylene glycol 4000, 6000, 20000, pentaerythritol, pentaerythrityl tetraacetate and acetic acid by fusion and solvent method. However, by fusion method (direct melting method) some active ingredients may be deteriorated when heating[17, 18].

Goldberg et al.[21,22] reported that increasing the dissolution rates of sulfathiazole, chloramphenicol and N-acetyl-p- aminophenol by forming solid solution and eutectic mixture with urea the solid solution system had greater dissolution rate than eutectic mixture. Both methods increased dissolution rate of poorly soluble drugs. Griseofulvin, by forming solid solution with succinic acid dissolved 6.5 to 7 times faster than pure drugs.

Mayersohn and Gibaldi[17] found that the solid state disperse of griseofulvin in polyvinylpyrrolidone resulted in five-to tenfold

increase in the dissolution rate of the drug. Even in the absence of wetting agent in the dissolution medium, the enhancement was still greater.

Stoll, et al.[23] studied the in vitro dissolution of coprecipitates of reserpine with cholanic acid derivatives in ethyl acetate at 37° C. An increase in dissolution rates of coprecipitates over that of pure reserpine was noted, due probably to a reduction in the particle size of reserpine during the formation of coprecipitates. The rate of dissolution of reserpine from the coprecipitates in a 1:16 molar ratio showed a rank order correlation with in vivo potency.

At room temperature and pressure, one polymorph may be thermodynamically more stable than the other form in the solid state. The metastable polymorph possesses a higher solubility and dissolution rate than does the stable form. With poorly soluble drug, it is possible to increase the solubility simply by modifying their crystalline nature[24,25].

Shefter and Higuchi[26] reported a comparative study on the dissolution behavior of hydrated and non solvated form of cholesterol, theophylline, caffeine, glutathimide, and succinylsulfathiazole. It was shown that the anhydrous forms dissolved more rapidly in water and in all cases yielded drug concentration in solution substantially higher than hydrate state. Conversely, they also reported that the solvated forms of fluorocortisone with n-pentanol or ethylacetate and of succinylsulfathiazole with n-pentanol dissolved much more rapidly than did non-solvated forms of the drugs.

Higuchi and Lach[27] reported the use of xanthine to form complex with drug resulting an increase in the solubility of drug. Higuchi, et al.[28] observed that the faster rate of dissolution for either compound occured when the molar ratio was 1:1 of benzocaine-caffeine complex.

Zoglio, et al.[29] showed that caffeine formed soluble complex with the ergot alkaloids.

Higuchi and Ikeda[30] prepared a rapidly dissolving form of digoxin by complexing the drug with hydroquinone.

Yang, et al.[31] studied the effect of amorphous silicon dioxide on drug dissolution by solvent deposition or ball milling with three commercial amorphous silicon dioxides. They found that the mixture containing amorphous silicon dioxide by both the ball milling and solvent deposition methods increased dissolution more than tablets containing pure poorly soluble drug.

Monkhouse and Lach[32] increased the dissolution rates of various poorly soluble drugs by adsorbing the drug onto an adsorbent and increasing the surface area of the drug in contact with dissolution media.

Mc Ginity and Harris[33] increased dissolution rates of poorly soluble drugs by adsorption to montmorillonite. A dramatic increase in dissolution rate was seen with prednisolone adsorbate and 100 percentage of the drug was presented in solution from the 1:4 adsorbate after four minutes.

The improved oral absorption of drugs when administered with surface active agents has been attributed to the improved solubility and dissolution rate due to solubilization and/or wetting effects of surfactant. Nogami, et al.[34] reported that the rate-determining step in

tablet disintegration was the penetration of media through the pores in tablet. An equation was derived to :

$$L^2 = \frac{r\gamma\cos\theta t}{2\eta} = kt \quad \text{.....(15)}$$

where

L = the length penetration at time "t"

k = the coefficient of penetration

r = the average radius of void space

θ = the contact angle

γ and η = the surface tension and visocity, respectively.

From the equation, a surfactant has two effects on penetration of liquid into tablet. The addition of a surfactant lowers the surface tension and decreases the contact angle. Thus, the overall coefficient of penetration of liquid into the tablet rises in present of surfactant and enhances disintegration. There are numerous publications reporting the effect of surfactant in dissolution medium and its enhancement of dissolution rate of hydrophobic drug. The addition of polysorbate 80 (Tween 80) to the dissolution fluid increased dissolution rates of benzoic acid[35], benzocaine[36], phenacetin, and phenobarbitol[37]. This effect was due to its ability to decrease interfacial tension between drug particles and dissolution media.

Mendell[38] studied the three most commonly used tablet disintegrants : corn starch, alginic acid, and microcrystalline cellulose (Avicel^R) by comparing with carboxymethyl starch for disintegration time. In direct compression, carboxymethyl starch was shown to be better disintegrant than the others for both water soluble and poorly soluble drugs.

Rubinstein and Price[39] studied the effect of disintegrants : Explotab^{R}, Polyplasdone^{R} XL, Amberlite^{R} IRP 88, maize starch, and Elcema ^{R}P 100 on bioavailability of furosemide 40 mg tablet. With maize starch and Elcema^{R}P 100, the drug was significantly less bioavailable than with the others. Tablet containing Explotab^{R} gave the highest bioavailability.

Kalidindi and Shangraw[40] studied about soy polysaccharide as a disintegrating agent. Soy polysaccharide performed well as disintegrating agent in direct compression formulation with results paralleling to those of cross-linked carboxymethyl cellulose at the 2 % level and superior to corn starch at 8 % level. The dissolution rates of the drug from tablets were rapid, particularly at the 5 % level.

Kalidindi and Shangraw[41] evaluated soy polysaccharide as a disintegrant in wet granulation utilizing both lactose and dicalcium phosphate dihydrate as fillers, gelation as granulating agent and hydrochlorothiazide as a model drug of low water solubility. It was found that soy polysaccharide was more effective than starch but less effective than cross-linked carboxymethyl cellulose (Ac-Di-Sol^{R}) at equivalent concentration.

Shangraw, et al.[42] reported the new disintegrating agents that would improved disintegration and dissolution without adversely affecting the tablet matrix. These agents swelled many times their original size when placed in water and at the same time produced minimum viscosity effect. They were classified as three major groups :

1. Modified starch, known as carboxymethyl starch or sodium starch glycolate : Primojel^{R} and Explotab^{R}.

2. Cross-linked polyvinylpyrrolidone : Polyplasdone^{R} XL

3. Modified cellulose, known as sodium carboxymethyl cellulose: Ac-Di-Sol^{R}, CLD^{R} cellulose, and Nymcel^{R}.

Gorman, et al.[43] found that Ac-Di-Sol^{R} enhanced dissolution rate of hydrochlorothiazide and pyridoxine. There was a report shown that 2 % Ac-Di-Sol^{R} enhanced dissolution rate of hydrochlorothiazide greater than 10 % Sta-Rx^{R} 1500 starch, 2 % Polyplasdone^{R} XL, and 2 % Explotab^{R} [44].

The disintegrating agent, Ac-Di-Sol^{R}, which is a modified cellulose gum, is an internally cross-linked form of sodium carboxymethyl cellulose. Ac-Di-Sol^{R} (Croscarmellose sodium) is a cellulose either produced by reacting alkali cellulose with sodium monochloroacetate under rigidly controlled conditions. Ac-Di-Sol^{R} differs from soluble sodium carboxymethyl cellulose only in that it has been cross-linked to ensure that the product is essentially water insoluble. Ac-Di-Sol^{R} is an highly absorbent and therefore provides excellent disintegration characteristic[45].

Figure 5 shows the structure of sodium carboxymethyl cellulose. It is visualized as a chain composed of repeating cellobiose unit.

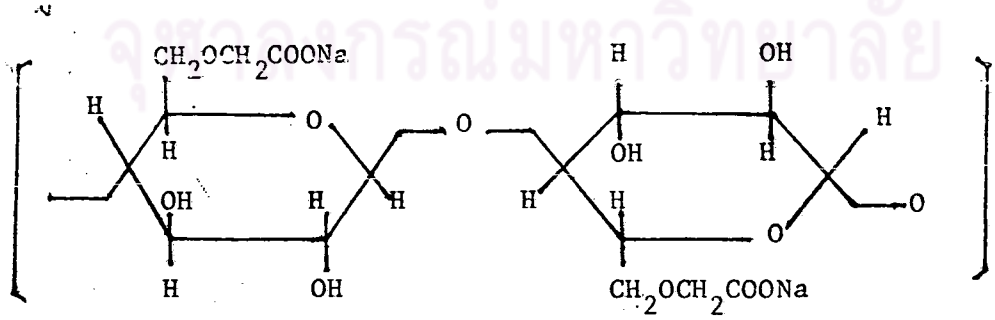

Figure 5 Idealized structure of sodium carboxymethyl cellulose. (degree of substituted of 1.0)[45].

Purposes of the study

The scope of this research is to study the influences of croscarmellose (Ac-Di-Sol^{R}) as disintegrating agent on the dissolution rates of three poorly soluble drugs, griseofulvin, prednisolone, and furosemide. The effect of croscarmellose concentration on dissolution rates of tablet will be investigated in order to elucidate the relationships. The tablets containing poorly soluble drugs were prepared by two different methods, dry granulation and wet granulation, to study the effect of processing on dissolution rates. The dissolution rates will be investigated and compared to the tablets containing Avicel^{R} PH 101, Polyplasdone^{R} XL, and Explotab^{R} as disintegrating agents. These tablets will be compressed in different hardnesses to investigate the effect of hardness on dissolution rate of poorly soluble drugs. To elucidate the relationships of the method of incorporating the disintegrating agent and dissolution rates, tablets will be prepared by incorporating the disintegrant by three different methods : intragranular, extragranular, and 50 % intragranular plus 50 % extragranular.

The reasons of selecting griseofulvin, prednisolone, and furosemide as the model drugs are due to their water insoluble properties and widely used in treatment. Griseofulvin, widespreadly used as an antifungal agent, is very slightly soluble in water. Its aqueous solubility is 15 mcg/ml at 37^{o} C[46]. This drug has been selected for many studied aimed at improving its dissolution rate and absorption[47-50].

Prednisolone, normally used as an orally corticosteroid, is practically insoluble in water. Its aqueous solubility is 1:3,000 at room temperature[51]. This drug has been selected for many studies aimed at improving its dissolution rate and absorption[52-54].

Furosemide, generally used as diuretics, is very poorly water soluble. It is practically insoluble in water (55).