CHAPTER II

REVIEW OF RELATED LITERATURE AND RESEARCH

Aspirin or Acetylsalicylic Acid

1. Description

Aspirin is acetylsalicylic acid, also called salicylic acid acetate and 2-(acetyloxy)-benzoic acid (50-78-2). Aspirin was first prepared by Bayer laboratory in 1897 and was marketed in tablet form in 1899. Aspirin was the first medicine to be produced in tablet form and the effects of this drug are still to be fully realized [12]. Basic structure of aspirin includes an ester, a carboxylic acid and a benzene ring (Figure 1). Aspirin has a chemical formulation of $C_9H_8O_4$.

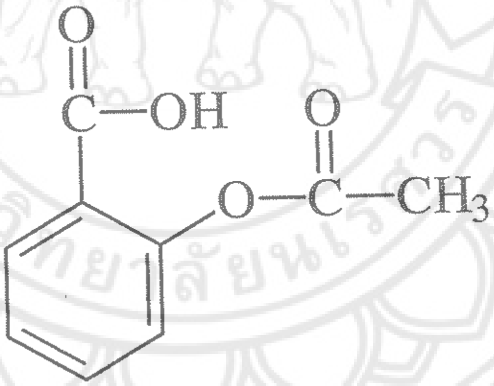

Figure 1. Structure of acetylsalicylic acid (M.W. 180.16)

Aspirin is a pain relieving drug. In medical term, aspirin is able to have the effect to block the production of a substance called Prostagladins which are produced by the body whenever a cell in the body is injured. Production and the release of these prostagladins lead to swelling, pain, fever and other symptoms commonly associated with injuries or diseases. Aspirin is renowned for producing the pain and fever relief by blocking the production of these prostagladins [12]. One of the most interesting new uses of aspirin is in preventing heart attacks. Aspirin inhibits blood platelets from clumping together to form blood clots. Aspirin thus reduces the chances of a blood clot in the coronary vessels which supply the heart with blood and reduces risk of stroke or clotting after surgery [13].

Aspirin was synthesized using salicylic acid and acetic anhydride with sulfuric acid as catalyst. Due to many disadvantages of salicylic acid such as very bitter tasting and caused irritation of the mouth and stomach lining, vomiting, and even respiratory failure at high dosages, Felix Hoffman who was a German scientist working for Frederick Bayer and Company synthesized salicylic acid to aspirin by changing the chemical composition of the molecule through a simple chemical reaction, i.e., combined salicylic acid with acetic acid [12]. Salicylic acid, the reactant, has two functional groups (common arrangements of atoms found in organic molecules). The first, the –OH group, indicates that the substance is an alcohol. The second, the carboxyl group (COOH) indicates that the substance is an organic acid. When the salicylic acid molecule reacts with acetic anhydride, the –OH group of the salicylic acid molecule combines with the acetic anhydride molecule, forming the byproducts of acetic acid and acetylsalicylic acid, or aspirin. The –OH group of the salicylic acid molecule has been replaced with the ester group, which results from the reaction of an alcohol (OH) and an acid (acetic anhydride). The ester group reduces the strength of the carboxylic acid and makes aspirin easier on the mouth and stomach [14]. The structure of salicylic acid showed in Figure 2 and the reaction of aspirin synthesis showed in Figure 3.

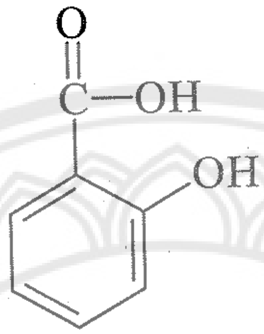

Figure 2. Structure of salicylic acid (M.W. 138.1)

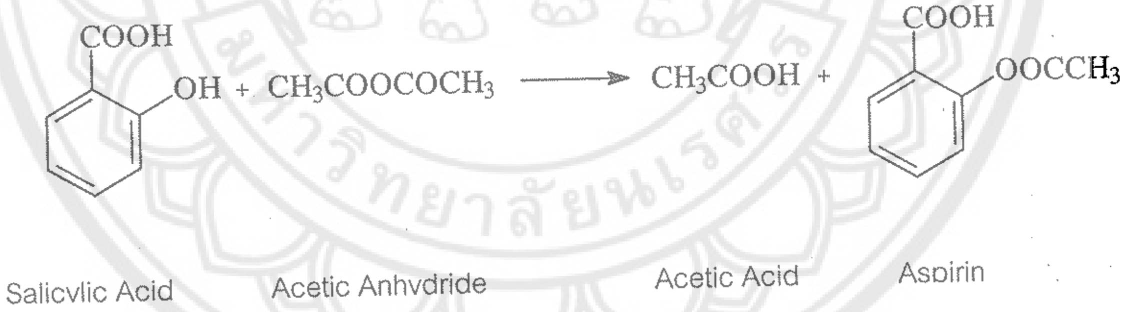

Figure 3. The reaction of aspirin prepared by chemical synthesis from salicylic acid, by acetylation with acetic anhydride

2. Physical Properties

Appearance

Aspirin is white crystals, commonly tabular or needle-like, or white, crystalline powder [15]. It is odorless, but might have a faint odor of acetic acid [12].

Solubility

Aspirin 1 g dissolves in 300 ml water, in 5 ml alcohol, 17 ml chloroform, or about 10-15 ml ether. It is less soluble in anhydrous ether or absolute ether. Solubility of aspirin is 0.0004 g/ml in carbon tetrachloride, 0.0033 g/ml in benzene, 0.1 – 0.2 g/ml in ether and insoluble in petroleum ether [12].

The solubility of aspirin in water depends on temperature. Aspirin dissolves with decomposition in solution of acetates and citrates, and in aqueous solutions of alkali hydroxides or carbonates [16]. The aqueous solubilities of aspirin at different temperatures are as follows: 1g in 300 ml at 25°C, in 100 ml water at 37°C, and in 33 ml at 100°C [15].

Dissociation Constant (pka)

Springer and Jones determined the dissociation in aqueous solution at various temperatures. At 25°C, they determined the dissociation constant as 2.8×10^{-4} (pka 3.55) [12]. The Merck Index gives a value of 3.27×10^{-4} (pka 3.49) at 25°C [17]. When the apparent pka was determined using quaternary butyl ammonium hydroxide as the titrant, the pka observed depended on the solvent of crystallization. From ethanol (m.p. 140-142°C), a value of 8.99; from hexane (m.p. 121-124°C), a value of 9.19 was obtained. The latter higher value was ascribed to internal hydrogen bonding of the carbonyl to the hydroxy group [12]. This apparent pka should not be confused with the true pka of 3.5 [15].

Partition Coefficients

When aspirin was partitioned between buffers pH 1-7 and octyl alcohol, partition coefficients ranging from k = 17.7 (pH 1) to k = 0.025 (pH 7) [12] or Log *P* (octanol/pH 7.4), -1.1 and Log *P* (octanol/pH 1.05), 1.2 [15] were obtained. Coefficients of 0.32 in toluene:water and 1.81 in chloroform:water were determined [12].

3. Solid State Stability

To generate information on which proposal for the shelf-lives of drug substances, stability testing for bulk drug substances is an integral part of preformulation development. Thus, a major concern of every drug manufacturer should be whether his/her product has the capability to retain its effectiveness and safety for the duration of its expiry. Moreover, stability testing for bulk drug substances was specified in guidelines of the Committee for Proprietary Medical Products (CPMP, code of CPMP/QWP/556/96) under the European agency for the evaluation of Medicinal Products (EMEA) in April 1998; and the World Health Organization (WHO), and it was specified in Food and Drug Administration of USA (FDA) draft in June 1998 [18].

Aspirin is a substituted phenyl ester. As an aromatic ester, it has a good leaving group, and is thus relatively unstable toward hydrolysis and other acyl transfers, as shown in Figure 7. Its pH-rate profile reveals specific acid and specific base of hydrolysis, plus a pronounced sigmoid curve that is the result of hydrolysis of aspirin anion. This species undergoes intramolecular general base catalysis (catalytic group being the ortho carbocylate), leading to a pH-independent plateau, from about pH 5 to 8, in the pH-rate profile, as shown in Figure 8. It is this phenomenon that accounts for the hydrolytic instability of aspirin in pharmaceutical formulations. Stability of aspirin in formulations is promoted by minimizing contact with water, with basic substances (e.g., carboxylate salts) and with nucleophiles (e.g., amines and hydroxyl group) [19].

Aspirin is stable in dry air. Aspirin undergoes hydrolysis to yield acetic acid and salicylic acid in contact with moistures or in aqueous solution [20]. The rate of decomposition [21] is both acid and base catalysed and is accelerated by heat. Maximum stability is observed at pH 2 and 3, as shown in Figure 8. Drug decomposition may yield toxic by-products which endanger the patient. The rate of aspirin hydrolysis reaction is said to be second order, since dependent upon the aspirin concentration and upon solution pH which is the hydronium ion concentration $[H^+]$ at solution pH values less than approximately 2.5 or the concentration of hydroxyl ion $[OH^-]$ at pH values greater than approximately 7.0. At pH = 7.5, the rate expression for the hydrolysis of aspirin may be written:

$$\frac{-d[A]}{dt} = K[A][OH^-] \qquad \text{.........................(1)}$$

Where,

[A] = the concentration of aspirin

[OH$^-$] = the hydroxyl ion concentration

K = the second order rate constant

t = time

If the solution is buffered so that the hydroxyl ion concentration remains essentially constant, the rate expression may be rewritten as:

$$\frac{-d[A]}{dt} = KC[A] \qquad \text{.........................(2)}$$

where,

C = the unchanging hydroxyl ion concentration

Since two constants can always be combined into one constant, the above expression is equal to:

$$\frac{-d[A]}{dt} = K_{app}[A] \qquad \text{..........................(3)}$$

Where,

$K_{app} = KC$

From the above equation, it can be seen that the degradation of aspirin in a solution buffered at pH = 7.5 will follow first order kinetics; that is, the reaction will appear to be a first order reaction, dependent only on the concentration of one reactant; i.e. aspirin.

The integrated form of a first order rate expression is:

$$\ln A_t = \ln A_o - K_{app}\, t \qquad \text{..........................(4)}$$

where,

A_t = the amount of drug remaining at time = t

A_o = the amount of drug initially present

K_{app} = the apparent first order rate constant

t = time of sampling

This equation is of the form:

$$y = mx + b \qquad \text{..........................(5)}$$

where,

m = the slope of the line

b = the y intercept

For the hydrolysis of aspirin in buffered solution (pH = 7.5) as shown in Figure 4, a semi-log plot of the aspirin concentration remaining versus time should yield a straight line with a negative slope equal to $-K_{app}$.

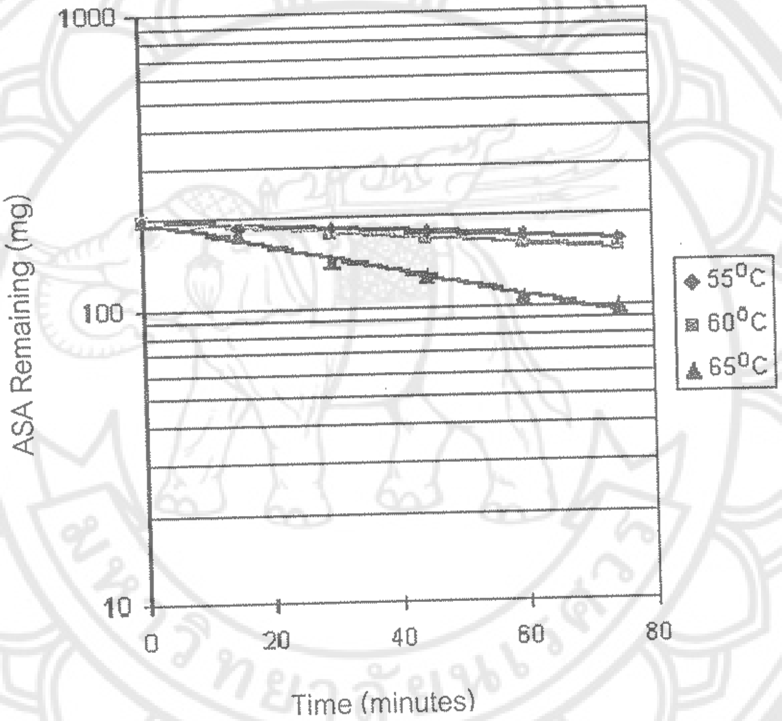

Figure 4. Aspirin degradation kinetics in buffered solution (pH = 7.5) at 55°C, 60°C, and 65°C

The experimentally determined first order rate constant (K_{app}) can be related to the true second order rate constant by the expression:

$K_{app} = K[OH^{-}]$ ....(6)

The pseudo first order degradation of aspirin in a solution buffered at pH = 7.5 can be followed by measuring the increasing concentration of salicylic acid spectrophotometrically.

One mole of salicylic acid is produced when one mole of aspirin degrades; so, using the ratio of the molecular weights of aspirin to salicylic acid, we can determine the weight of aspirin degraded for each mg of salicylic acid produced.

$$1\, mg\ salicylic\ acid \times \frac{180.15\ g\ /\ mol\ aspirin}{138.12\ g\ /\ mol\ salicylic\ acid} = 1.304\, mg\ ASA \qquad \text{... (7)}$$

Thus, each milligram of salicylic acid present represents the degradation of 1.304 milligrams of aspirin. Since the amount of aspirin initially present is known and since the amount of aspirin which has degraded can be determined, the amount of aspirin remaining can be calculated.

The shelf-life or expiration date is the length of time required for the product potency to be reduced to some percentage of its original value. For most products, this is the T_{90} or time at which the product retains 90% of its original potency. Although the drug's stability at room temperature is of primary interest, a stability study at room temperature would take too long to be useful as a screening procedure for new formulations. Therefore, such screening studies are conducted at elevated temperatures in accordance with the Arrhenius equation:

$K_{app} = Ae^{-Ea/RT}$ ....(8)

where,

K_{app} = the apparent rate constant for the reaction
A = the frequency factor
E_a = the activation energy for the reaction
R = the gas constant (1.987 cal./deg. mole)
T = absolute temperature (degrees Kelvin)

The Arrhenius equation can be rewritten as:

$$\ln K_{app} = \ln A - \frac{E_a}{R} \cdot \frac{1}{T} \qquad \text{..........................(9)}$$

Again, an equation of the form y = mx + b is generated, indicating that a semi-log plot of K_{app} versus the reciprocal of the absolute temperature (1/T) should yield a straight line with a negative slope equal to $-E_a/R$ as shown in Figure 5. This line can be extrapolated to the value of 1/T that corresponds to room temperature and the predicted rate constant for the reaction at room temperature can be taken from the y- axis.

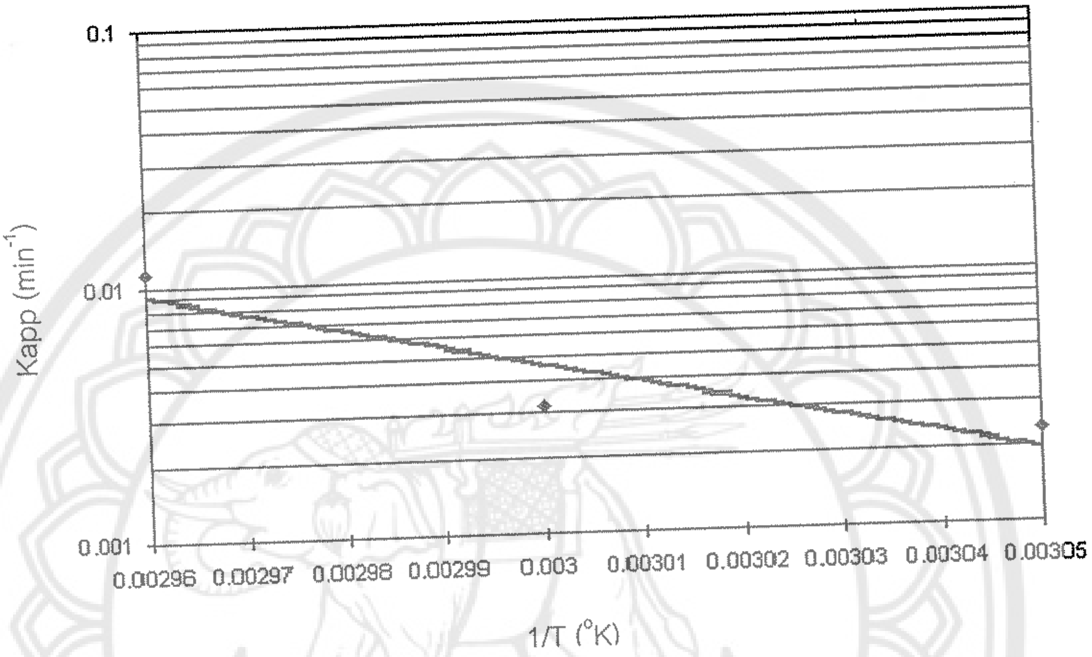

Figure 5. Arrhenius plot for aspirin hydrolysis at pH 7.5

Although the degradation of aspirin in a solution buffered at pH = 7.5 occurs too slowly at room temperature to be adequately studied during one laboratory period, the reaction proceeds rapidly at temperatures of 50°C and above. The reaction will be conducted at approximately 55°, 60°, and 65°C.

Michael, James & Won [22] studied the stability of aspirin in a moisture containing direct compression tablet formulation. Stability samples were assayed for aspirin and salicylic acid using a stability indicating analytical method. Analysis of the stability data showed that the rate of aspirin decomposition accelerated with time. Also, the aspirin decomposition rate increased with temperature. The data were fit to the empirical equation $y = 100 - kt^n$, where y is the percent aspirin remaining, t is time, and k and n are constants. The formulation showed good stability, with less than one percent decomposition occuring after 1.75 years of storage at room temperature. This result indicates that although the aspirin formulation contained approximately 8 percent moisture, at room temperature the majority of the moisture present in the formulation is not available to react with the aspirin. The apparent activation energy of the solid-state aspirin decomposition was 46 kcal/mole, which is higher than expected. This result may be due to a temperature dependent release of moisture from the Emdex^R (a mixed-sugar diluent containing approximately 8 percent moisture). Researchers suggested that the further studies were needed to verify this explaination.

4. Degradation and Products

All of the decomposition reactions of aspirin in pharmaceutical systems are acyl transfers. Hydrolysis is the most important of these. The solid samples of aspirin decompose by a route involving physical adsorption of water from the atmosphere to the solid surface, dissolution of aspirin in adsorbed layer, and acid-catalyzed hydrolysis of the dissolved aspirin. In the absence of water no decomposition is observed [19]. Decomposition of aspirin results from hydrolysis of the ester group, with the end products being salicylic acid and acetic acid as shown in Figure 6. Researchers who have made a thorough study of the hydrolysis of aspirin under various well-controlled and sated conditions reported that the reaction is very complex [23].

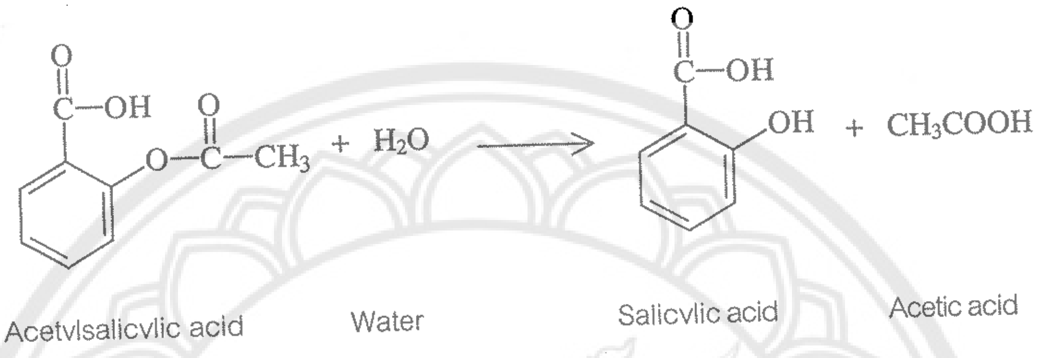

Figure 6. Equation of acetylsalicylic acid hydrolysis.

The pH-rate profile for aspirin hydrolysis, measured by Edwards, showed that the transition state for hydrolysis in the pH-independent region involves the aspirin anion, either alone in a unimolecular reaction or together with one or more molecules of solvent. Three mechanisms were consistent with this kinetic result for intramolecular catalysis of hydrolysis of aspirin by the carboxyl group:

1. A unimolecular process in which the carboxylate group acts as a nucleophile. There was no longer any evidence that specifically supported the nucleophilic mechanism. It was not consistent with the effect of substituents on the reaction, and there were several indications that the rate-determination step was not a unimolecular process.

2. A general acid catalysis of the attack of hydroxide ion by the undissociated carboxylic acid group, this mechanism was rejected because intermolecular general acid catalysis by the carboxyl group of aspirin should be observed for attack by acetate as well as by the hydroxide ion (Figure 7).

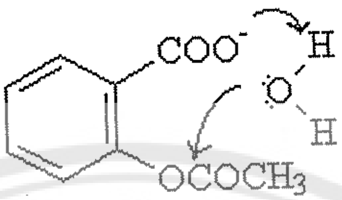

Figure 7. Participation of the ortho-carboxylate group in the hydrolysis of aspirin

3. A general base catalysis of the attack a water molecule by the carboxylate anion. There seems little doubt that the intermolecular reaction of acetate with the aspirin anion represents general base catalysis. There is even less doubt that intramolecular catalysis of hydrolysis by the carboxylate group of aspirin involves the same mechanism as the intermolecular reaction with acetate ion.

In actuality, it seems probable that the aspirin reaction lies close to the borderline between nucleophilic and general base catalysis [23].

A complete and thorough kinetic study of the factors involved in the hydrolysis of aspirin in dilute solution (3×10^{-3} *M*) was conducted by Edwards. Using a UV spectrophotometric method for simultaneous determination of aspirin and salicylic acid, he observed the rate of decomposition to be first order at a fixed pH value (between pH 0.53 and 12.77) and constant ionic strength at 17°C. Figure 8 showed the relationship between velocity (rate) constant and pH. This curve was subject to only slight alteration with change in ionic strength. Temperature dependence of this aspirin reaction was studied between 10°C and 50°C. The pH-rate profile was of the same shape for every temperature, with displacement upward with increasing temperature.

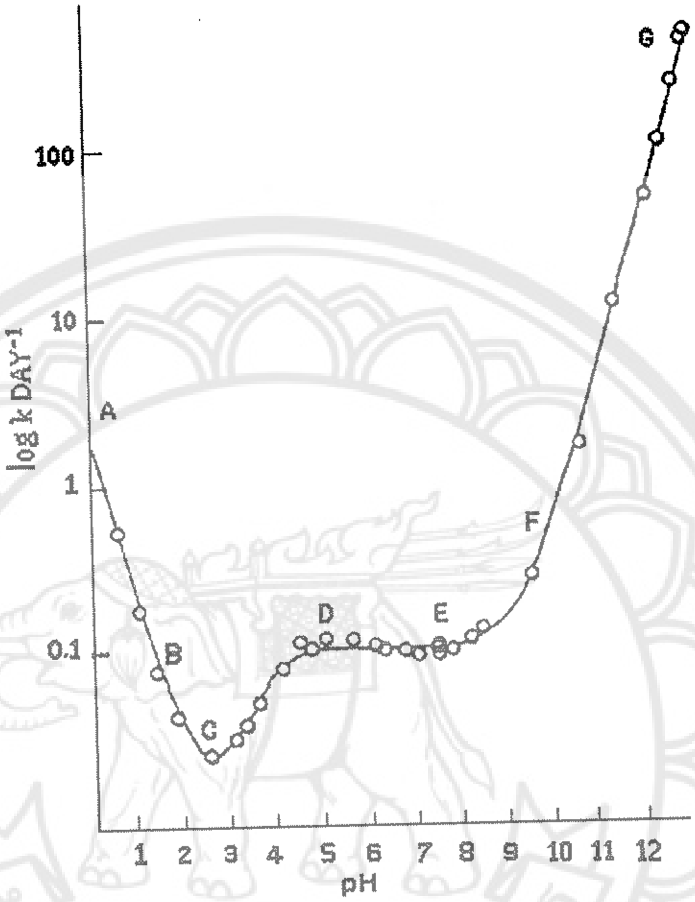

Figure 8. pH-rate profile for hydrolysis of aspirin at 17°C

In Figure 8, this plot of log *k* against pH helps to show visually that the hydrolysis was catalyzed appreciably by hydrogen ion (section AB of figure) and very strongly by hydroxyl ion (section FG of figure). Over the pH range 5-8 (section DE of figure), the rate was constant; in the pH range 2-3 (section C of figure), there was a pronounced minimum rate where the reaction velocity dropped to less than a quarter of the stationary value (DE) which is usually taken to represent the "spontaneous reaction."

In a number of reports, degradation products of aspirin were investigated by various analytical methods such as UV spectrophotometer, spectrofluorometer, thin-layer chromatography (TLC), High-performance Liquid Chromatography (HPLC), mass spectrum (MS), Capillary Electrophoresis, and Near-IR.

Pilatluck, Achara & Chaipat [24] determined salicylic acid, the degradation product of aspirin, in analgesic-antipyretic sachets containing aspirin as the active ingredient by UV spectrophotometer using wavelength at 230 nm for acetylsalicylic acid and at 530 nm for salicylic acid. The results obtained from this study showed that the increasing of non-compliance samples was age-dependent, i.e., greater amount of salicylic acid in analgesic-antipyretic sachets with the longer-aged samples. The percentage of non-compliance samples with the age of 1-12 months, 13-24 months, 25-36 months and more than 36 months were 14.6%, 17.6%, 64.3% and 100%, respectively. In addition, it was also found that there were 25.4% were not conform to the registered specification.

Ulla Reidl [25] determined acetylsalicylic acid, salicylic acid, and metabolites in biological fluids by high-performance liquid chromatography. The results were found that aspirin rapidly hydrolyzed to salicylic acid in the human body. According to the plot of concentration against time showed in this study revealed that plasma concentration of salicylic acid was greater than maximum concentration of acetylsalicylic acid, at 20 minutes. Moreover, the amount of salicylic acid increases progressively and reached maximum at 50 minutes. The degradation was due to aspirin was attacked by water.

5. Compatibility of ASA with Some Excipients

In pharmaceutical dosage formulation, excipient compatibility studies are routinely performed to look for possible interactions of a formulation component with an active ingredient both physical and chemical interaction. In particular, the solid dosage forms such as tablets and capsules, usually contain diluents, binders, disintegrants and lubricants. Aspirin [15] produces a sticky mass when it is triturated with acetanilide, amidopyrine, phenacetin, phenazone, hexamine, phenol, salol, potassium acetate, or sodium phosphate. Aspirin is incompatible with free acids, iron salts, phenobarbitone sodium, quinine salts, potassium and sodium iodides, and with alkali hydroxides, carbonates, and stearates. In admixture with salts containing water crystallisation, hydrolysis of aspirin is occurred. Solutions of alkali acetates and citrates, as well as alkalis, dissolve aspirin but the resulting solution rapidly hydrolyses to form salicylic acid and acetic acid. Aspirin has been reported to acetylate other drugs such as paracetamol, homatropine, ephedrine, phenylpropanolamine, and codeine phosphate in solid admixture. Aspirin has also been reported to be incompatible with antihistamines. Excipients that have been used in uncoated aspirin tablet are aluminium glycinate, calcium carbonate, cellulose, colloidal silica, ethylcellulose, hypromellose, lactose, magnesium carbonate, pregelatinised maize starch, saccharin sodium, sodium lauryl sulphate, and triacetin [15].The physicochemical study on the interaction between an active ingredient and selected excipients must be considered [26]. A number of investigations showed that the presence of some excipients could interfere the dissolution and absorption of drugs such as microcrystalline cellulose, kaolin, magnesium trisilicate and activated attapulgite [27], [28].

Gamal et al. [26] studied the molecular behaviour, dissolution characteristics and chemical stability of aspirin in preparing pharmaceutical powder dosage forms. It is found that interaction of Di-O-methyl-β-cyclodextrin (DMβCD) and aspirin resulted in a high water soluble excipient. X-ray diffraction analysis, differential scanning calorimetry (DSC), infrared (IR) absorption spectroscopy of powder mixture, and dissolution test were used to investigate the physicochemical properties, such as dissolution characteristics and decomposition rate of aspirin of vary powder forms, which the ground mixture was in amorphous state and the inclusion complex was in crystalline state. The results obtained from the dissolution tests indicated that the DMβCD ground mixtures dissolved fast but in the case of inclusion complex the dissolution rate was extremely low. The dissolution rate is known to depend upon crystallinity, crystal form and other physicochemical parameters (Higuchi and Pitman, 1973). The results of the effect of the excipient, DMβCD, on the stability of aspirin showed that the aspirin molecules were dispersed monomolecularly, which results in an increase in the number of reaction sites, and leads to enhanced decomposition of aspirin in both powders, in the ground mixture and in the inclusion complex [26].

DSC is one of the most valuable instruments in the formulation study to give reliable information about possible incompatibility of materials. The results of DSC studies demonstrated that aspirin was incompatible with magnesium stearate due to thermal events could be detected while stearic acid which was compatible with aspirin did not give any thermal events in this method [29].

In many cases, extensive drug excipient reaction studies can cover solid-solid reactions which constitute an important aspect of the stability of formulations during development and prevent instabilities in final formulations. There is one of solid-solid reactions in formulation, that is, *transacylation*. The transacylation in this paper describes tablet mixtures containing aspirin and drugs with easily-acelated functionalities react to give acyl compounds and salicylic acid. NMR and X-ray method were used in this study. The results indicated that there is the reaction (hydrolysis) of phenylephrine hydrochloride with aspirin. This reaction an acetyl group is transferred from acetylsalicylic acid to the phenylephrine. For example, mixtures of phenylephrine hydrochloride and aspirin contained 80% of acylated phenylephrine after 34 days at 70°C. Adding starch and magnesium stearate slowed this acylation to about 1% in 34 days, while adding magnesium stearate alone resulted in complete decomposition in 16 days. Some diacylated product was also obtained. This reaction may proceed by direct acylation. In sumilar, aspirin tablets containing codeine or acetaminophen also yielded acylated drugs upon heating [30].

For hydrophilic excipients, sodium starch glycolate, croscarmellose sodium and hydrophobic excipients, crospovidone, colloidal silicon dioxide, they were found to cause interaction with aspirin. The interactions were due to condensation in the vicinity of the aspirin crystals after blending. When these excipients are combined with aspirin, even at relatively low level, the character of the excipient has a profound effect on the sorption of the blend. The results of photomicrographic evident demonstrated that both sodium starch glycolate and croscarmellose sodium appear as remarkably hydrophilic substances which swell considerable with moisture uptake. In the case of sodium starch glycolate, hydrophilic effect to aspirin particles is so pronounced that condensation is restricted to areas surrounding the particles. The influence of crospovidone in the aspirin powder blend on the condensation is quite different from that of the other disintegrants. The crospovidone is less water soluble, there are even some stable droplets in contact with the crospovidone particles, and the crospovidone does not swell after 24 h exposure to 100% RH. There is evident that some of the hydrophobic effect noted before, a low level of water sorption by the hydrophobic drug was responsible for the apparently unexpected stability, still exists. For another hydrophobic excipient, it is proof that the colloidal fumed silicon dioxide does not protect aspirin from contact with water. In fact, droplets of water may be seen in contact with aspirin crystals. The excipients added to aspirin perturb the orientation effect to different degrees. Sodium starch glycolate and croscarmellose sodium are so hydrophilic such that they overwhelm all other influences. In fact, they serve as particulate nuclei for condensation. The ultimate chemical stability of aspirin is never improved by combination of the drug with a hydrophilic excipients [31].

The study of the mechanism of degradation of dry aspirin was carried out. Aspirin tablets with 1% magnesium stearate and corn starch in 5 mg increments were subjected to differential thermal analysis (DTA) and thermogravimetry (TG), both before and after exposure to water. A decrease in the endotherm relating to the melting of aspirin in tablet form was shown and, in general, a further diminution occurred following water treatment. This might be due to a decreasing surface area effect upon compaction and to a dissolution effect, also causing a diminished surface area upon water treatment. The most obvious change could be cause by the liberation of water from the excipient, which then reacts with the aspirin component. With increasing concentrations of corn starch the stages of degradation of aspirin were shifted to higher temperatures. Aspirin in tablet form was shown to be stabilized in the presence of increasing amounts of corn starch. These and related studies on the shelf-life of pharmaceutical products indicate possible interactions between the active ingredient and other ingredients of product formulation [32].

Influence of Material Properties on Dissolution rate

Include manufacturing, storage, the quality of raw material could cause varieties in properties of drug products. The different sources of raw material may provide the variation in characteristics of raw materials [33], [34], [35]. The physicochemical properties in relation to the dissolution rate of drug were significantly effected by some characteristics such as surface morphology, degree of porosity, surface area, particle shape and particle size of a drug [35]. The dissolution properties of a drug are crucial in determining its bioavailability [36].

1. Effect of Drug Particle Properties

It is well known that the particle size of bulk powder has great effect on dissolution rate of sparingly soluble drug such as indomethacin. Puttipiparkhachorn, Mitrevej & Papangkornkij [33] investigated the variation in powder characteristics of indomethacin obtained from three sources in Thailand. The results in this study showed that dissolution rate of indomethacin powder increased with decreased in particle size.

Likewise, a group of Simóes [37], [38] studied the influence of particle size of indomethacin powder on dissolution rate. The researchers concluded that particle size of indomethacin had strong influence on dissolution.

For crystalline drug, dissolution process is determined by a variety of other properties of drug particle such as surface morphology, degree of porosity, surface area, particle shape and particle size [36].

On the one hand, the reduction of particle size in order to expose larger surface area to the dissolution medium is the obvious choice for improving dissolution of poorly water-soluble drugs such as griseofulvin, norfloxacin, chlothalidone and spironolactone [39], [40], [41], [42].

Many papers [43], [44], [45], [46], [47] demonstrated the effects of particle size distribution and particle shape on dissolution performance. It is generally expected that fine powder has a faster dissolution as compare with coarse powder. However, some cases such as orthoboric acid powder with a high fine content, has lower rate of dissolution than orthoboric acid crystal having larger particle size [35].

Farin & Avnir [36] determined the parameter that reflected the morphology of the surface, which participated actively in dissolution process. This active surface needs not coincide with the total surface of the particle. Such situations may be found in highly porous materials where the active dissolution take place only in the outer, exposed regions of the particle. It may be found in sparingly soluble drug, where the dissolution process active at sites of imperfection in the crystalline structure. In both cases, the collection of active surface sites is a subset of all surface points, with a fractal dimension of its own. Particularly difficult to assess quantitatively are the degrees of surface irregularity and roughness, and their effects on the dissolution rate of drugs. María-José Fernández-Fernandez-Hervás et al. [48] described the use of fractal geometry in the study of morphology and dissolution behavior of diclofenac-hydroxyethyloyrrolidine salt. The fractal dimension and reactive dimension reflects a dissolution process strongly influenced by the size particle. Moreover, controlling the geometrical parameter of the salt can increase the efficiency of the dissolution process.

2. Effect of Polymorphism

There are many papers [49], [50], [51], [52], [53], [54] reported that some characteristics (for example, melting point, crystal shape, density, hardness, solubility, optical, electrical properties, etc.) vary with polymorphic form. Polymorphism is the ability of compounds to crystallize into more than one structure. There are many substances in the European Pharmacopoeia which reported to have polymorphism [53]; for example, phenylbutazone, indomethacin and chloramphenicol. Therefore, drug substances, having polymorphism and obtained from various sources, should be investigated for their polymorphism. Dissolution rates of drugs are determined partly by crystal forms. Some polymorphs have identical dissolution rates, while others vary to a great extent. For example, the polymorphic pairs of both mercaptopurine and disopyramide and three of four polymorphs of tolbutamide have been found to have similar dissolution rate. However, on the other hands, polymorphs of chlopropamide, acetohexamide, and phenylbutazone displayed diverse dissolution rates [54].

In the effect of polymorphism on dissolution rate, Gecse et al. [55] studied the gastrointestinal absorption of two polymorphic forms of aspirin, form I and form II. The structural changing of these two forms was identified by differential thermal analysis (DTA) and thermal gravimetric analysis (TGA). The dissolution rate of form I was higher than form II. Similar with this paper on this effect are the three forms of iopanoic acid [56], two forms of mefenamic acid [57].

Shibata et al. [58] reported the physicochemical properties of cimetidine polymorphism, three anhydrous forms (A, B and D) and monohydrate form (C). Among the three anhydrous forms of cimetidine, form A was thermodynamically more stable than the others. IR spectroscopy and X-ray powder patterns were used to confirmed the structural conversion of form C into form A on dehydration. The dissolution rate constant for form C was about 1.29, 1.70, and 1.90 times greater than those for forms A, D, and B, respectively. The results obtained by these two different methods showed clearly that form C is more soluble in deionized water than the other forms. Kokubo et al [59] investigated the bioavailability of cimetidine polymorphs in rates. The results of this study exhibited that there was a similar relationship among crystalline forms with respect to dissolution testing. In conclusion, form C, among the four kinds of cimetidine crystalline forms, had the highest bioavailability and dissolution rate constant.

Researchers reported phenylbutazone exists in several polymorphic forms. Thermal analysis, X-ray diffraction, IR spectroscopy, and solubility studied were used for identification and characterization of different crystalline modifications of phenylbutazone [60]. Tuladhar and co-workers determined the effect of five different polymorphic forms (A, B, C, D and E) of phenylbutazone on dissolution rate [61], [62]. Among the five phenylbutazone polymorphs in a comparative study [61], form C showed a maximum dissolution rate, almost 55% higher than that of form A, while forms B and E displayed about 20 and 35% higher dissolution rates than form A, form A and form D were very similar in rates of dissolution. In the effect of crystal form on dissolution of phenylbutazone tablet, two polymorphic forms of the drug (form A and B) were studied [62]. The results demonstrated that form B with 6 μm particles have the longer $t_{80\%}$ in comparing with form A, because under compression for form B; 6 μm particles bond to a greater extent than those of form A.

3. Effect of Pseudopolymorphism

As the same previous description, the ability of compounds to crystallize in more than one structure is termed polymorphism, and an extremely large number of molecules have been found to exhibit the phenomenon. Numerous compounds are capable of forming other nonequivalent structures through the inclusion of solvent molecules in the crystal lattice. When these alternate crystal structures originate from the incorporation of solvent molecules, many workers use the term pseudopolymorphism to identify this class of structural variation [51]. There are many compounds of pharmaceutical interest forming solvates include theophylline, cortisone, fluprednisolone, flucortolone, chlordiazepoxide and caffeine as well as antibiotics such as ampicilin and erythromycin. The ability of a drug to form solvate can largely increase the number of available possibilities for modifying and controlling process, dissolution, stability and bioavailability. Allen et al. investigated the different solution behavior of erythromycin, monohydrate, dihydrate and anhydrate. The results exhibited a significant different in dissolution rate of the dihydrate as compared to the monohydrate and anhydrate. Researchers also revealed this behavior that the dissolution rates are probably related to particle-particle interactions and/or wettability of the various hydrates of pharmaceutical compound [63].

4. Effect of Crystal Habit/Morphology.

Crystal habit and the internal structure of a drug can affect bulk and physicochemical properties, which range from flowability to chemical stability. Habit is the description of the outer appearance of a crystal [64]. Crystal habits may influence on several pharmaceutical characteristics such as tableting behavior, dissolution of crystalline material, and suspension syringeability [50]. In tablet behavior, to evaluate it as influenced by crystal habit, Shell in 1963 quantitatively described crystal habits by measurement of preferred orientation and related this parameter to compression characteristics of the powder. He took the radio of the relative peak intensities of critical lines in the X-ray diffraction pattern and used them as average habits of crystals. In this study, he found that the higher the 001 orientation ratio to the 010 orientation, the better was the tableting behavior. In the dissolution of crystalline material, he mentioned that if the a crystal changes its habit due to crystal poisoning by a dye, then, in an indirect way, the absorbed dye may inhibit the dissolution of drug crystals, which may affect the bioavailability of the material, reported by Piccolo and Tawashi in 1973.

In addition to the study of effect of particle size on dissolution rate, Tromelin et al. studied the effect of two commercial qualities of orthoboric acid, labeled crystals (A, B and C) and powders (A, B and P), on their dissolution rate. The results showed that the dissolution rate of crystals (A, B and C) and powder (A, B, and P) appeared very different. The A, B and C quality dissolved for more rapidly than the bulk A, B and P quality [35]. In spite of their different names, two commercial qualities of orthobiric acid are related to the same crystal network [65]. The morphology and nature of solid surface also play an important role on dissolution issues, and they were recently studied using geometry. Moreover, the dissolution process is determined by a variety of other properties of the drug particles such as surface morphology, degree of porosity, surface area, particle shape and diffusion constant of the dissolved material. On the other hand, the degree of surface irregularity and roughness can produce some effects on the dissolution rate of drugs [36], [48].

As some excipients, magnesium stearate, which used as lubricant in solid dosage forms, may be believed for the effect on drug release of drug products. It is well known that magnesium stearate can decrease the dissolution rate of a drug because of combining by magnesium stearate, which acts as a water reciprocation [66], [67]. Both concentration and its surface area influence the extent of decreasing in dissolution rate [66]. Frattini & Simioni [68] investigated for the variation in characteristics of magnesium stearate from the various sources, demonstrated that there is the tablet differing in disintegration time and dissolution of formulations using magnesium stearate from three sources due to having the difference in specific surface area.

Factors Affecting the Properties of Uncoated Tablet [69], [70], [71], [72], [73]

Uncoated tablet is a solid dosage form, make by compaction of a tablet formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug products. The uncoated tablets are convenient, easy to use, portable, and less expensive than other oral dosage forms. These are the reasons for the number of uncoated tablets manufactured today. There are many factors that influence on the process of tablet formulation, which result in the varying performance or quality of tablet products such as appearance, weight uniformity and drug release (disintegration and dissolution) These factors as follows:

1. Powder Characteristics for Tablet Compressing

Lack of requiring a critical approach to ingredient selection, flow properties, blending, and segregation can lead to the variation in tablet properties such as dosage uniformity, stability, timely drug release (disintegration and dissolution), and bioavailability. McCarty [69] demonstrated that the problems with variation and reduction in dissolution rate of tablet formulation cause by most drug substances do not inherently have such properties. They often segregated in powder blend processing. These problems were solved by formulating drug substances with excipients. There are two most common processes that were always used. There are ① granulation and ② direct powder blends (DPB). High dose drugs that have poor flow, low bulk density, or lack compressibility are not good candidates for direct powder blends. Granulation can overcome many inadequacies inherent to the individual components of a formulation, as granulation changes these into a completely different material. The magnitude of inherent resistance of powder material is influenced by many factors including:

(a) Surface energy changes and elastic deformation properties, influence individual particle true areas of contact;

(b) Plastic deformation likely occurs to some extent in powder beds depending on the applied load, and almost certainly it occurs during the compaction of powders into tablets;

(c) Electrostatic forces can also play a role in powder flow depending on the insulating characteristics of the material and environmental conditions;

(d) Particle shape and size distribution have all been shown to influence flow and compaction as well.

Ideally, the powder used for tablet compressing requires good flow properties. Furthermore, they are required to produce even packing density; for example, the particle of each component is required to have density as close as possible to avoid segregation, and powder should not be cohesive. The important powder characteristics of tableting are following:

1.1 Powder Flow

Powder flow is most frequently thought of as relevant to formulation development. There is a number of measures of powder flow to the manufacturing properties of a formulation. In particular, the importance of physical properties in affecting powder flow has been well documented. However, research into the effect of the mechanical properties on powder flow has been very limited. It is of equal importance to determine the powder flow characteristics of bulk drug early in the development process (preformulation phase). There are many methods used to investigate bulk powder flow as well:

1.1.1 Angle of Repose

The angle of repose (ϕ) is a method used for measuring the internal cohesive and frictional effect in a loose powder. It is a simple practical technique for measuring resistance to particle movement. The angle of repose is the angle (ϕ) as defined by the equation:

$$Tan\phi = \frac{2h}{D} \qquad \text{........................(10)}$$

where h is the powder bed height, and D is the powder bed diameter. It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. Experiment methods of determining angle of repose (ϕ) may be divided into two groups, static and dynamic methods, and some of these are shown in Figure 9.

(1) Static methods are the methods which fixed funnel and free standing cone, and fixed bed cone;

(2) Dynamic methods are the methods which tilted box, rotated cylinder and drained angles of repose.

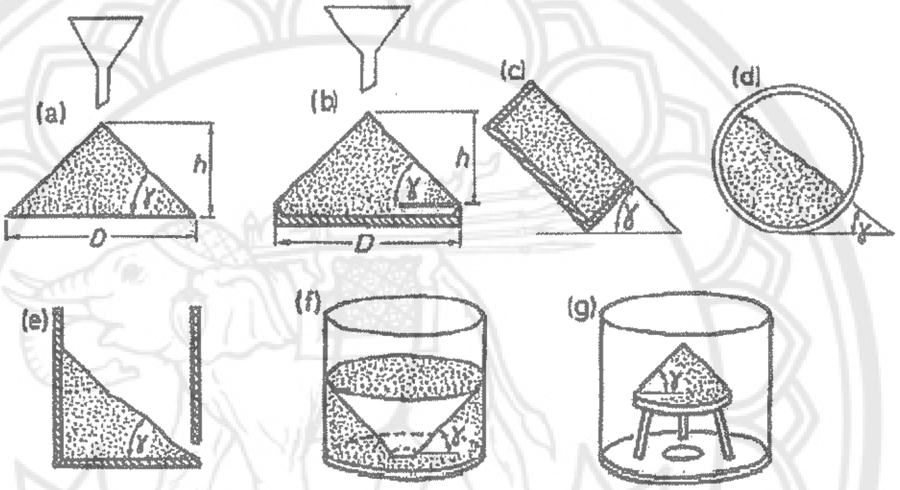

Figure 9. Methods of measuring the angle of repose (ϕ or γ shown in figure). (a) fixedfunnel and free standing cone, (b) fixed bed cone, (c) tilting cylinder, (d) rotating cylinder, (e,f,g) apparatus to measure the drained angle of repose.

1.1.2 Flowmeter

The flowmeter is made up of a hopper which powder flowed on to a pan that is supported by a strain-gauged arm. When examining the flow properties of a powder, the first type of flow, static flow, has been investigated extensively.

Apart from two common method groups described above, i.e., static methods and dynamic methods, the other methods are "flow through aperture" and "flow from hopper", also used to measure powder flow.

1.2 Bulk Density

In the development of tablet formulation it is necessary to determine the density of the mixture of powders and the individual component, which is formulated into the tablet formulation. Knowledge of the density of a powder is important in determining the volume that a specific weight of material will occupy. Further, powder that differ significantly in density will have a tendency to segregate, resulting in non-homogeneous blends. In addition, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds. Two commonly used indexes are calculated from density of powder: the Hansner index and Compressibility or Carr index which are popular methods used to predict powder flow.

1.3 Cohesion

Cohesion results in the drag or frictional forces acting within a powder bed which prevent powder flow. There are many methods used to measure cohesion and other characteristics such as shear strength and tensile strengths. Although measurements of cohesive properties of powder may be an useful guide, the results of these experiments may not always be reliable. Finally, it must be supplied proof of the properties including powder flow. This yields reproducibly filled of tablet die which improves weight uniformity and allows tablets to be produced with more consistent physicomechanical properties.

The presence of molecular forces produces a tendency for solid particles of powders to stick together. This causes the powders not flow freely. The flowability of powders depends on the state of consolidation, which in turn is determined the stresses acting on the powder. The development of this concept requires the use of the Jenik shear cell, or the use of annular shear cell. Data derived from the shear cell experiments yield locus of the material can be plotted and, by extrapolation, the cohesion obtained from the intercept on the y axis. In rheological terms, the stress due to cohesion along the yield locus may be called the yield stress and the powder termed a plastic solid.

The largest use of powder pharmaceutically is to produce tablets and capsules. Together with mixing and compression properties, the flowability of a powder is of critical importance in the production of pharmaceutical dosage forms. One of the reasons for producing free-flowing pharmaceutical powders is the uniform feed from bulk storage containers or hoppers into the feed mechanisms of tableting equipment, allowing uniform particle packing and a constant volume-to-mass ratio which maintains tablet weight uniformity.

There are many industrial processes which require powders to be moved from one location to another. This is achieved by many different methods such as gravity feeding, mechanically assisted feeding, and pneumatic transfer. In each of these examples, powder is required to flow. The flowability is dependent on both process design and particle properties.

2 Formulation of Uncoated Tablet Product

The formulation for the uncoated drug tablet is developed in consideration of uniforms of solid medicaments prepared by compaction. The uncoated tablet consists of a mixture of powders that are compacted in a die to produce a single, and rigid body. Ideally, for this type of tablet, all ingredients are intended to be swallowed whole and then disintegrate and release their medicaments in the gastrointestinal tract (GIT) [74].

It is certainly true that quality must be built into the uncoated drug tablet. A critical element in building quality into drug tablet is in the design of the granulation or direct compression system from which the drug tablets are made. The uncoated tablets are heterogeneous system and they are one of the most complex classes of drug products from a physical sense. Achieving satisfactory drug dissolution profile is more difficult from tablets than from any other class of oral dosage form. It is widely recognized that the physical and mechanical properties of tablets may undergo aging following an exposure to environmental stress. Thus, a stability profile that affects bioavailability and other fundamental tablet properties may be occurred. Therefore, it can be seen that the physical and mechanical property stability profiles can be as important as, if not more important than, the chemical stability of the tablet product. It is also apparent that attempts to optimize tablet formulations can only be as successful as the accuracy and adequacy of the physical methods used in the product evaluation. In order to ensure the drug release from an uncoated tablet and adequate bioavailability when formulating this formulation, it is necessary to consider the processing conditions, material and equipment used. Also, the skills of the personnel employed in the manufacturing step is needed to be concerned [75].

2.1 Drug Solubility

Since a drug must normally be in solution before systemic absorption can take place, drugs given via oral administered must dissolve in the contents of the gastrointestinal tract. Thus, the rate of dissolution of drugs in gastrointestinal fluids could influence the rate and extent of absorption of those drugs. In as much as the rate of dissolution of a tablet drug is a function of its solubility in the dissolution medium, the latter could influence absorption of the relatively insoluble drugs [76]. This means, unless other factors dominate the rate-controlling step in the absorption process, the rate of drug solubility is the rate at which the drug is transferred from the solid state into solution. Hence, the lower the drug solubility, the lower the rate of dissolution and so absorption will be.

Te Wierik, Eissens & Lerk [77] found that the solubility of drug controls the disintegration and dissolution process. It can be confirmed that the disintegration time tend to increase with an increase in solubility of a drug product. Disintegration is caused by water penetration into the tablet causing the disintegrant to swell. With drug which soluble in solution media (diazepam in 0.1N HCL solution) it might come to a competition between the drug particles, which need to be dissolved, and the disintegrant particles, which need to be swell.

In order to increase the drug solubility and dissolution rate, coprecipitates of the low solubility drug are prepared; for example, coprecipitates of sulphathiazole and polyvinylpyrrolidone (PVP) [78] as well as coprecipitates of danazol and hydroxypropyl β-cyclodextrim [79].

One of the points of view of the drug dissolution, formulators may require to consider the solubility of both the filler and the drug. For instance, few tablets intended for oral administration are totally soluble in aqueous media, but if such a product is needed, then soluble excipients (or soluble fillers) are employed. It is revealed that the release of drug from tablets formulated with soluble excipients may be more prompt than from those formulated with insoluble excipients. The soluble excipients include dextrose, lactose, mannitol, and sodium chloride [74].

2.2 Particle Size

An increase in dissolution rate from tablet can be attributed to an increase in surface area in contacting with the solvent by reducing the particle size of the drug and/or excipients. There are numerous researches that reported the effect of particle size of some active ingredients on dissolution or bioavailability [80] such as rifampicin [81].

Abdul-Fattah, & Bhargava [80] investigated the effect of particle size in solid dispersions of drug tablet on dissolution rate and its aqueous solubility. In this study, the halofantrine (a free base drug) was formulated in solid dispersion with various water-soluble carriers, and this drug was also made into different particle size distribution during preparation of the dispersions. The results showed the significant effect of particle size on drug release. A high dissolution rate and solubility was occurred by the reduction in particle size of the drug.

The particle size has significant effect in synthesis of pharmaceuticals because it has a significant effect on the applicability of a particular delivery system and/or the pharmaceutical action of the drug. If the product obtained from the actual synthesis does not meet the stipulated requirements, post-synthesis processing such as ball milling may be necessary for size reduction. Particle produced by ball milling commonly possess a broad particle size distribution [82]. Hintz & Johnson [83] concluded that the extent of milling of drug affected the dissolution rate and the amount of drug absorbed orally. Their conclusions are from estimating the effect of the particle distribution of drug contained in three solid formulations which differed only in the extent of milling of drug used to make the formulations.

An increase in surface area for dissolution of drug by decreasing the particle size, may reduce the contact between the liquid and the solid. Thus it may not always necessary increase the dissolution rate by making smaller particle size. In this case, a wettability is the important property regarding to the formulation and processing of tablets as well as other solid dosage forms. The wetting of surface is applied to many pharmaceutical powders which do not wet readily due to their hydrophobic nature and surface active agents to increase the hydrophilic nature of these powders. The methods used to increase the wettability of powder are as follow: granulating with a binder, coating with a hydrophilic powder, and spray drying with acacia [84]. For example, the formulation technique involves the conversion of the hydrophobic surface of griseofulvin to the hydrophilic character by treating with a film-forming polymer. This enhances the wettability of powder, and increases its dissolution rate [85]. An alternative method of increasing the wettability of a solid formulation is to the incorporation of a hydrophilic material [86].

2.3 Granulation

Granulation may be considered the opposite of size reduction, i.e., particle growth. According to the current technology, granulation may be defined as particle agglomeration. Undoubtedly, granulation is known to increase the dissolution rate of fine particles. In this case a solvent is only binder, so there is no change in contact angle, only the particle arrangement is treated. Conversion of hydrophobic drug surface to a more hydrophilic character by granulation with a (water-miscible) binder, by spray-drying with acacia, or by coating with a hydrophilic material resulting in enhanced dissolution rates [87].

Bolhuis, Zuurman & Te Wierik [88] investigated the effect of granulation with super disintegrant on dissolution rate of tablets. The results showed that the dissolution rate of tablets containing granulation with very high concentration of super disintegrant was slower than tablets containing granulation with high concentrations of super disintegrant. It is postulated that this effect is caused by the formulation of a viscous barriers of the super disintegrant in the very high concentrations in the granules during the dissolution process.

Granulation can improve the compression characteristics of the drug, densify material, render the material free flowing, and control the rate of drug release. Gao et al. [89] studied the feasibility of producing tablets by fluid bed granulation technique of a high dose, poorly water soluble, low density, and micronized drug comparing with a high shear granulation method of the same drug. This study demonstrated that wet granulation tablets of this drug could be manufactured using fluid bed technique. With a proper adjustment of process variables, dissolution rate of the tablets from the fluid bed granulation method was comparable to dissolution rate from the optimized high shear granulation process. Moreover, in the fluid bed granulation, granules from this process were more porous, less dense and more compressible than the granules from the high shear granulation process. The difference in the granulation compressibility could be attributed to the difference in the granule porosity. However, the high shear granulation process produced granules with better flow properties than the fluid bed granulation method.