CHAPTER II

LITERATURE REVIEW

Pharmaceutical Solid

Solid state chemistry of drug substance, particularly organic compound, has been systematically studied over a long period of time. It has shown a wide variety of states of solid compound. Polymorphism is one the most well known of the different state of molecular arrangement. It is not only polymorphism which is very important and strongly impacts on various pharmaceutical issues, but molecular adduct as well. The differentiation of drug in solid state presents a different in physical, chemical and physicochemical properties. Subsequently, the dosage form performances with different polymorph will show dissimilar therapeutic effects.

Classification of Pharmaceutical Solid (Haleblien, 1975)

According to Figure 2.1, it is a common and classical dichotomous key of solid state classification. Starting from solid compounds, they can be separated as two main categories. Crystalline structure is employed for primary differentiation of potential solid. They are discriminated in terms of crystalline habit and internal structure, respectively. Crystal habit means the description of outer appearances of interested solid. Several terminologies are used to define each crystal habit such as acicular, blade, tabular, plate etc. The habit of solid particle is one of the most important factors in unit operation of pharmaceutical manufacturing. For example, acicular or blade crystal usually generated the content uniformity problems during powder mixing. The injection of suspension with plate shaped crystal is easier than that of needle shape crystal. Moreover, dissimilar crystalline habit also gives unequal dissolution rate.

On the other hand, internal structure is also pivotal issue of the solid compound. Solid crystal is the result from the molecular arrangement of active moiety with binding forces and geometry. Thus, the uniform of molecular packing in crystal lattice unit is called crystalline state whereas non uniform or short-range order of arrangement is defined as amorphous solid. The difference between crystalline and amorphous is clearly defined by X-ray powder diffraction (XRPD). Halo pattern is a

specific character of amorphous phase that shows a wide spread of low reflected x-ray intensity over entire degree of 2 theta. Nowadays, amorphous solid arise an important in pharmaceutical formulation. Several potential drugs in dosage form are found to be amorphous because of their high water solubility which gives solubility and bioavailability better than crystalline state. The high water solubility of amorphous dealt with non uniform molecular arrangement that provides the high molecular mobility and high reactivity with water of hydration.

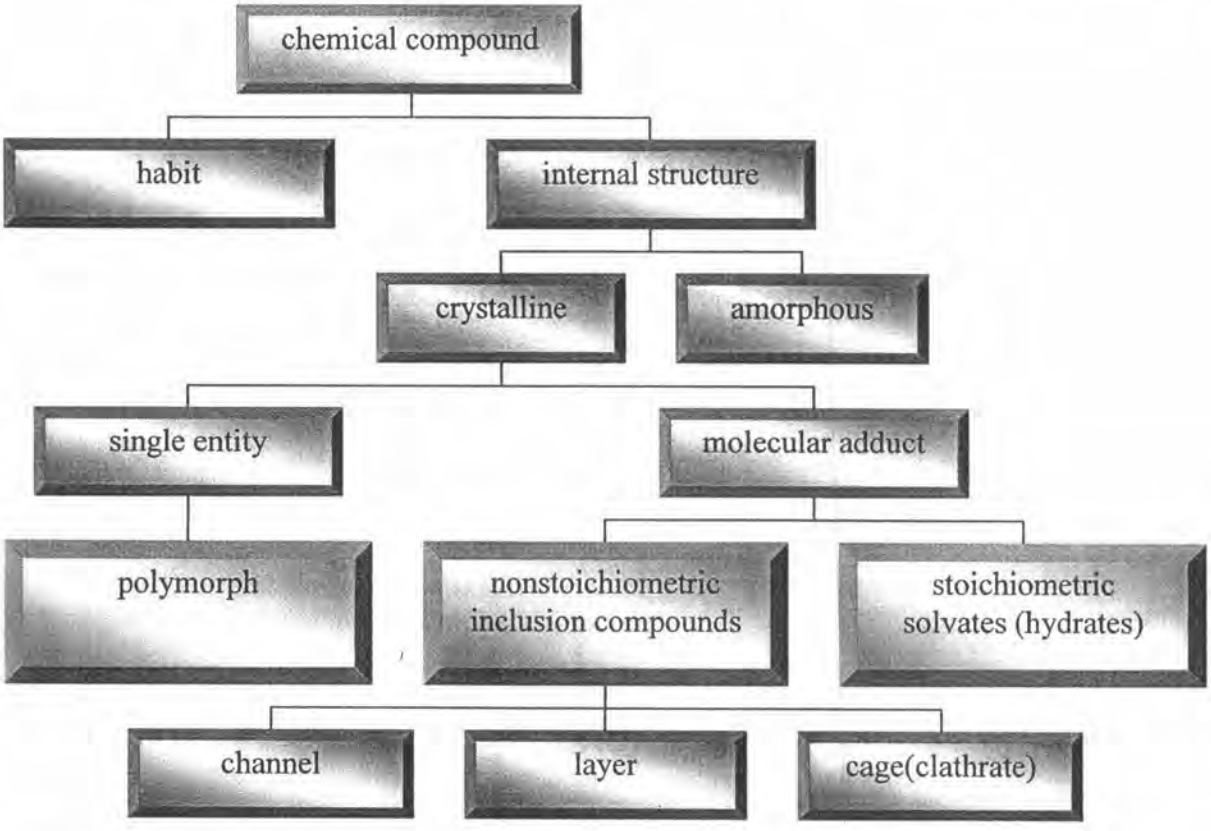

Figure 2.1 Classification of solid state material

Crystalline solid comprises of drug molecules that are uniformly packed in unit cell. Each drug molecule is placed in a wide array among three-dimensional space and provides a difference in arrangements. The dissimilar molecular packing in crystal unit is called polymorphism. Polymorphism is very important not only for its physicochemical properties but also its drug availability. Each polymorph has individually specific characters, resulting in different physicochemical and biopharmaceutical properties. Chloramphenicol palmitate is an early example of polymorphic issue (Haleblien, 1969). Form B of chloramphenicol palmitate is an

active form whereas Form A is an inactive form. The different ratio of Form A to Form B gave unequal plasma drug concentration after oral administration. The higher the amount of active Form B provides higher plasma drug level. There are many other cases of polymorphic transformation which affect dosage form performances. The product recall of ritonavir soft gelatin capsule from world market during post marketing surveillance was unavoidable due to the conformational polymorphic transformation problem (Chemburkar et al. 2000).

In addition, the combination of drug molecules and other species such as organic solvent or cocrystallizing agent can also exhibit crystalline structure. The entrapment of organic solvent especially during recrystallization is called solvate (Görbitz and Hersleth, 2000). If water is entrapped, the solvate will be named "hydrate" (Byrn et al., 2000). Meanwhile "co-crystal" is defined as the state which other small molecules (non solvent) are included and occupied the space in the original crystal unit (Almarsson and Zaworotko, 2004; Peterson et al., 2006). The combination of fluoxetine HCl and small organic acid molecules had been designed base on the concept of co-crystal (Childs et al., 2004). The organic acids were held in crystal lattice via hydrogen bonding due to an interaction between specific functional group of host and guest molecule. The co-crystal of fluoxetine with different organic acids showed significant difference in intrinsic dissolution rate.

Polymorphism and Pseudopolymorphism (Byrn et al., 1999; Giron, 1995)

Molecular arrangement of a compound can exhibit in a wide variety of array depending upon molecular structure. Differentiation in three dimensional molecular packing is well known as "polymorphism". Polymorphism is mainly focused only on the molecular structure of its active moiety. However, in some circumstance, other species can stay in the active molecular structure with sustainable stability. This condition is well defined as molecular adduct. If solvent molecule is the guest, it is defined as "solvate". Meanwhile, if guest molecule is water, it is defined as "hydrate". Recently, the terminology of "pseudopolymorphism" can be used instead of solvate or hydrate. It is due to the ability of different molecular arrangements of the adduct similar to that of polymorph. However, dissimilarity amidst similarity between polymorphism and pseudopolymorphism are concerned with the type of molecules in the crystal lattice.

Pharmaceutical Application of Polymorphism and Pseudopolymorphism (Byrn et al., 1999; Khankari and Grant, 1995)

The use of different polymorphs of the pharmaceutical compound usually shows different dosage form performances. Thus, selection the right polymorph with suitable formulation will give a good stability and dosage form performances.

In general, pharmaceutical hydrate has lower water solubility than anhydrous form due to dissimilar thermodynamic activity. The use of pharmaceutical hydrate as a starting material is rarely performed because the formulation may fail upon dissolution test. However, there are some evidences which demonstrated the superior property of hydrate than that of anhydrous form. The hemihydrate form of paroxetine hydrochloride had higher degree of moisture stability than anhydrous form (Buxton et al., 1988). Metal salt of fenoprofen in the form of hydrate had a good stability against moisture (Hirsch et al., 1978). Cefixime trihydrate showed good chemical stability in worse case condition. In addition, the loss of water of crystallization in cefixime trihydrate structure induced thermal instability (Kitamura et al., 1989). Furthermore, the desolvation of prednisolone solvate illustrated higher degree of degradation under oxygen filled condition (Byrn et al., 1999). Eventhough hydrate basically has lower water solubility but it still has other advantages to be considered for dosage preparation. The physical stability of triazinoindole suspension was improved by preparing with hydrate form to avoid caking during storage (Caldwell, 1973).

Particle Size Reduction: Importance and Method of Preparation

One of the most important unit processes in the pharmaceutical industry is particle size reduction. It is due to the fact that the uniformity of blending between active pharmaceutical ingredients and other excipient is a very critical parameter which affects the quality of the final products. An inappropriate particle size and size distribution of each ingredient may generate several problems during manufacturing such as suspendability, bioavailability, inhomogeneity, segregration, electrostatic property, content uniformity of dosage unit (Venables and Wells, 2001), delivering capacity of respiratory drug delivery (Chow et al., 2007). Thus, the particle size is one of the key factors that strongly impact on pharmaceutical unit operation.

Several methods are utilized to decrease the particle size of materials. The most common unit operation for size reduction is comminution or grinding. It is a

very useful method with less time consuming. Furthermore, it can be employed to produce small particles in the industrial scale. Although there are a lot of advantages from grinding, several problems sometimes occur. For example, the fusion of particles due to high temperature generated may happen. The contamination from foreign material, including microorganism, also possible during grinding. Moreover, polymorphic transformation (Crowley and Zografi, 2002) and amorphization at the surface of comminuted powder (Brodka-Pfeiffer et al., 2003; Mosharraf and Nyström, 2003) are also the main problem during grinding. It is due to the high-energy input which induces crystal defect during grinding. The small particle size with partial amorphous phase of comminuted powder resulted in improved water solubility and appropriate for dosage preparation. However, amorphous material is thermodynamically unstable due to its higher energy state and commonly provides chemical instability. The water solubility of amorphous material in dosage form is reduced after storage because the transformations of amorphous phase to a more stable crystalline form (Crowley and Zografi, 2002). Therefore, the method of particle size reduction with minimal amorphous is the most desirable approach.

The new concept to obtain small particles is based on the assembly at the molecular level. Controlled-crystallization has been utilized to make a small particle from the molecular state of active moiety by crystallization inhibitors such as polymer or surfactant (Steckel, Rasenack and Müller; 2003). This is a very successful method to obtain smaller particles. Eventhough controlled-crystallization is more effective than grinding due to lower level of amorphous phase, traces of crystallizing inhibitor may be found either co-crystallized or adsorbed on the outer surface of particles produced and less applicable in an industrial scale.

There is an interesting alternative method of particle size reduction that is by desolvation. It is studied by several research groups and shows the potential of particle size reduction.

Desolvation Induced Particle Size Reduction

Desolvation generally occurs under specified condition. The crystallographic properties of desolvated material can be altered after desolvation. There are theoretical results of four different classes of crystallographic behaviors after desolvation (Byrn et al., 1999).

Class I: Materials can undergo a thorough change in their crystallographic properties. It will exhibit a different molecular arrangement that can be investigated by X-ray powder diffractometry (XRPD).

Class II: Partial change in crystallographic behavior after desolvation. This change will show only a slight shift in the XRPD pattern

Class III: The original lattice structure of solvate is still preserved even when solvent molecules are completely removed. It is known as "isomorphic desolvate". (Stephenson et al., 1998).

Class IV: Amorphization took place during desolvation due to rapid loss of solvent inducing a short range order in crystal structure during lattice loosening before rearrangements. Halo-like pattern of XRPD is observed in this situation.

In general circumstance, most organic materials will behave as Class I after desolvation. Structural integrity of desolvated materials may be perturbed and leading to structural collapse. According to the desolvation or dehydration induced particle size reduction, the progress of reaction compose of several steps.

1. The free water molecules are generated by breaking the bonds between active moiety and the water of hydration.
2. The diffusion of free water molecules from the void space within the crystal lattice toward the external surface of the solid particles.
3. The durability of the final dehydrated lattice structure is an important step to determine the possibility of structural collapse. If the particle size reduction occurs, one may be assumed that the structure of dehydrated crystal lattice is very weak. On the other hand, the dense and compact of crystal lattice after dehydration signifies stable structure and the size of particles are retained.
4. The final step of dehydration is concerned with the transformation of the dehydrated original structure to the lowest energetic anhydrous phase.

Therefore, the energy needed to generate the smaller particles is equivalent to the summation of the energy in the first and second step of dehydration. However, this energy is not directly used to reduce the particle size because the particle size reduction is the consequence after the second step of dehydration which depends on the durability of the dehydrated lattice structure. Thus, the amount of energy used for the particle size reduction is defined as the sum of the energy used in the first and second step and is an apparent value. Meanwhile, the total energy of dehydration is

equal to the overall energy of reaction which can be determined from the energy used in every step for complete dehydration.

Thermal dehydration for particle size reduction was first found 20 years ago. It was called "phase conversion from solvate to ansolvate method" (Sekiguchi et al., 1976). The basic concept of this method dealt with the desolvation of solvate by using either high temperature or reduced pressure to remove solvent from crystal structure. Structural collapse of crystal might occur and finally resulted in smaller particle size after desolvation. Griseofulvin chloroformate, several solvates of sulfonamide, ammoniated chloramphenciol and solvates of some barbiturate were some examples for particle size reduction by desolvation technique (Table 2.1). Solvates of organic solvent in which frequently used during crystallization were used as starting materials. However, organic solvents are not environmental friendly which potentially generate critical problems during solvent removal while desolvation. Therefore, water was an alternative solvent that was used instead of organic solvents to reduce the above problem. There was an also opportunity to reduce the particle size of hydrates by dehydration similar to previously reported solvates. Beclomethasone dipropionate monohydrate (BDM) was an example of hydrate which the particle size could be reduced during thermal dehydration. The changes in particle size of other compounds upon desolvation are summarized in Table 2.1.

Table 2.1 Desolvation/dehydration induced particle size reduction of certain solvate/hydrate compounds

CHEMICAL	SOLVENT MOLECULE	DESOLVATION METHOD	REFERENCE
barbiturate group	ammonia	↑temp + ↓pressure	Sekiguchi, 1978
sulfonamide group	ammonia	↑temp + ↓pressure	Sekiguchi, 1974
chloramphenicol palmitate	ammonia	↑temp + ↓pressure	Tsuda, 1980
	pyridine	↑temp + ↓pressure	
chloramphenicol	ammonia	↑temp + ↓pressure	Himuro, 1971
	chloroform	↑temp + ↓pressure	Sekiguchi, 1964
griseofulvin	benzene	Freezed drying	Suzuki, 1979
	dioxane	↑temp + ↓pressure	Sekiguchi, 1976
beclomethasone dipropionate (BD)	water	↑temp (isothermal)	Amolwan, 2001
risedronate sodium	water	↑temp, desiccation	Lester, 2006

Factor Affecting the Particle Size Reduction during Desolvation

1. The crystallographic property of solvate

Crystal packing of solvate, particularly host and guest (solvent) interaction in crystal lattice plays a key role on desolvation and offers a possibility for particle size reduction after desolvation (Byrn et al., 1999)

Host-guest interaction can be roughly indicated as two aspects. Firstly, guest molecule can be entrapped and occupied the space inside the crystal lattice by various interaction forces eg. Van der Waals interaction, electrostatic interaction including hydrogen bonding. In the case of hydrate, water molecules usually locate in pocket or void space of the lattice unit via hydrogen bonding. Water composed of one oxygen atom and two hydrogen atoms which behave as hydrogen bond acceptor and donor. Atoms in water molecule can accept or donate electron to the other function groups of host and form hydrogen bond. The strength of hydrogen bond always plays a critical role in desolvation. The strong hydrogen bond needs high energy of desolvation to destroy all the binding forces. In an attempt to predict the difficulty of desolvation of solvates, crystallographic arrangement of solvate and its ansolvate should be addressed. The molecular packing of host and guest in the lattice structure indicates molecular connectivity between host molecules midst guest molecules and demonstrates intermolecular bonding. The strength of hydrogen bonding between host-guest can be used to evaluate a difficulty of desolvation. Therefore, the knowledge about bonding force in the solvate is useful data to estimate the partial energy needed to induce a dehydrated original structure which may show the possibility of particle size reduction by desolvation.

Additionally, the fit of guest molecule into the pocket space of crystal lattice is also considered. Perlovich et al. (1998) recommended that the proportion of guest molecular volume over total void volume in the crystal lattice or "packing coefficient of a channel" related to the heat of desolvation and might correlate with a difficulty of desolvation.

According to the desolvation of solvate, general chemical reaction is presented as follow:

$$[\text{Host} + (\text{solvent})_n] \xrightarrow{\text{desolvate}} [\text{Host}] + n(\text{solvent})$$

The packing coefficient of a channel was calculated according to equation below

$$K_{chan} = \frac{(ZnV_{solvent})}{\Delta V}$$

where

K_{chan} is the packing coefficient of guest molecules in channels of active molecule matrix

Z is defined as the number of structure units of solvate in a unit cell

n is the number of molecules of a solvent

$V_{solvent}$ is molecular volume of solvent

and ΔV is the change of the unit cell volume of the solvate during desolvation process

The lower K_{chan} indicates less difficult to desolvate. It can be described that the lower K_{chan} directly means the large free void space compared to the occupied solvent volume. Thus, solvents are easy to move around their occupied space and are readily impeded from the lattice unit with less energy. Furthermore, the large void space also provides a long distance between host and guest and eventually resulted in loose binding. Consequently, host-guest interaction can be easily overcome. Lester et al. (2006) found that partial dehydration reduced the particle size of risedronate sodium hemipentahydrate. One molecule of channel type water in hemipentahydrate structure was definitely removed by low temperature drying. On the crystallographic point of view, the unit cell volume and Z of risedronate sodium hemipentahydrate were 2,677 $Å^3$ and 8, respectively. Meanwhile, the unit cell volume of dehydrated risedronate sodium was 1,223 $Å^3$. Therefore, the difference between unit cell volume of hemipentahydrate and partial dehydrated structure of risedronate was equal to 1,454 $Å^3$. Based on the molecular volume of water is 10 $Å^3$ (Chakarvarty, Bhinge and Varadarajan, 2002); K_{chan} of risedronate sodium hemipentahydrate was mathematically found to be 0.137. This lower K_{chan} indicated that the water molecule in risedronate sodium hemipentahydrate structure took up less space in the lattice unit and had more chance of leaving from the crystal lattice. The lattice integrity was altered and generated an unstable crystal structure when certain dehydration energy was applied. Hence, the original structure of crystallite would be destroyed and finally collapsed.

2. The particle size of solvate

Different particle size of BDM directly affected the final particle size of BD after heating (Chinapak, 2001).

3. The number of solvation and desolvation cycle

One cycle of sorption and desorption of chloramphenicol palmitate ammonia solvate provided a smaller particle size than intact solvate form. The maximum of size reduction ability was obtained after two cycles of sorption and desorption. However, the more sorption-desoprtion cycle (3 to 5 cycles) did not result in a significantly smaller particle (Tsuda et al., 1980).

4. Method of desolvation, dehydration temperature and dehydration time

By using thermal dehydration, the temperature level and time which it was exposed, affected the final particle size of solvates (Sekiguchi et al., 1974).

Solid State Kinetic (Byrn et al., 1999)

In general, solution state kinetics was studied and was well established and served as basic platform for solid state reaction kinetics. Solution state kinetic assumed a homogeneous reaction which is easy to derive a common rate equation of reaction. Meanwhile, it is very difficult to make a homogeneous hypothesis in solid state. It is due to the fact that the starting positions of solid state reaction usually occur at the defect site of solid material and do not consistently happen throughout the solid of interest. However, the mathematical models are based on different hypothesis for solid state reactions and yield the different solid state kinetic equations.

There are two important factors that must be well defined prior to the determination of the activation energy (E_a). They are fraction reacted (α) and reaction time (t). The plot of α versus t can be expressed in two different curves (Figure 2.2). The left curve in Figure 2.2 has a noticeable induction period before the reaction progress whereas the right curve does not have an induction period.

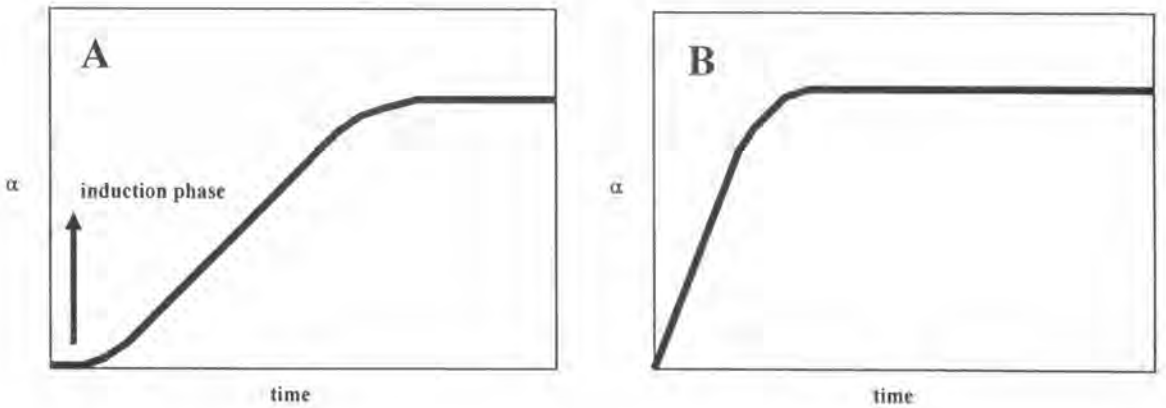

Figure 2.2 Typical α-t curves of solid state reactions (A, solid state reaction with induction period and B, the reaction without induction period)

The mathematical models for solid state kinetic are divided into four major groups depending on different assumption of mechanism.

A. Reaction involving nucleations

In this case, two equations are derived and commonly used.

The Prout-Tompkins equation: It is assumed that the reaction is controlled by linearly forming of reaction nuclei and continuously grows as a chain reaction. It is then terminated more rapidly with respect to an increment of nuclei.

$$\ln\left(\frac{\alpha}{1-\alpha}\right) = kt + c \qquad \ldots(2)$$

where k is rate constant and c is constant

The Avrami-Eroféev equation: It is assumed to be governed by random nuclei and progressively occurs in three dimensions and ingests other nuclei.

$$[-\ln(1-\alpha)]^n = kt \qquad \ldots(3)$$

where the value of n = ¼, ⅓, ½, ⅔ and 1.

B. Reaction controlled by phase boundaries

If the formation of reaction nucleus is not the main mechanism behind a reaction, there are cases that advancement of phase boundaries from the outside controls the step of reaction. It can be categorized along with the dimension of reaction as 3 groups.

One-dimensional advancement: the reaction is assumed to happen only in one direction of phase growing boundaries and then the rate of reaction depends upon only reaction time. The zero order kinetic equation is alternatively applied instead.

$$1-\alpha = kt \qquad \ldots(4)$$

Two-dimensional advancement: Two directional ways of the reaction, from outside of circular disk or cylinder inward, to be assumed for phase growing boundaries. This relationship is also known as "contracting area" equation.

$$1-(1-\alpha)^{1/2} = kt \qquad \ldots(5)$$

Three-dimensional advancement: On the one hand, if phase boundaries reaction is taking place around the sphere inward in three dimensions, the equation is changed to "contracting volume" equation.

$$1-(1-\alpha)^{1/3} = kt \qquad \ldots(6)$$

C. Reaction controlled by diffusion

The reaction in this model must be involved with gaseous species either from starting material or product of the reaction. In the same way with phase boundaries reaction; one, two and three dimensional advancement by diffusion controlled are derived as well.

One dimensional diffusion

$$\alpha^2 = kt \qquad \ldots(7)$$

Two dimensional diffusion

$$(1-\alpha)\ln(1-\alpha)+\alpha = kt \qquad \ldots(8)$$

Three dimensional diffusion

$$1-\tfrac{2}{3}\alpha-(1-\alpha)^{2/3} = kt \qquad \ldots(9)$$

A simplified model of three-dimensional diffusion is also known as "Jander equation"

$$\left[1-(1-\alpha)^{1/3}\right]^2 = kt \qquad \ldots(10)$$

D. Other equations

Power-Law equations

There is no theoretical basis for this equation, but still has been popularly used to analyzed the solid state kinetics and other kinetic of reactions.

$$\alpha^n = kt \qquad \ldots(11)$$

where the value of n = ¼, ⅓, ½, and 1. If the n value is equal to 2, one-dimensional diffusion equation is developed.

Equations based on the concept of reaction order

By using the concept of order that usually employed for solution state kinetic, reaction order: the sum of the exponents of concentration terms in rate law, equation are derived as following

Zero order reactions

$$1-\alpha = kt \qquad \ldots(12)$$

First order reactions

$$\ln\alpha = kt \qquad \ldots(13)$$

Second order reactions

$$\frac{1}{(1-\alpha)} = kt \qquad \ldots(14)$$

Derivatization of model kinetic reaction provides the solution of the determination of rate constant (k). It will be then lead to the calculation of Activation energy (E_a) along with the arrhenius equation. The correlation between k and the reciprocal of temperature level is well identified under arrhenius assumption as following.

$$k = Ae^{-\frac{E_a}{RT}} \qquad \ldots(15)$$

or

$$\ln k = \ln A - \frac{E_a}{R}\cdot\frac{1}{T} \qquad \ldots(16)$$

The plot of ln k versus the reciprocal of absolute temperature (1/T) gives a straight line with the negative slope of ($-E_a/R$) and the intercept of pre-exponential or frequency factor (A).

E_a means "a physicochemical quantity that represents the barrier for a chemical reaction" (Byrn et al., 1999 and Laider, 1984). Due to the fact that E_a is given by the slope of the straight line of ln k versus 1/T relationship, the steeper the slope or the higher the E_a the stronger the temperature dependence of the "rate of reaction" (Atkins and Paula, 2002). Generally, E_a has a positive value and directly indicates the temperature dependency of the reaction rate. However, the E_a has a possible to be negative value for the complex mechanism reaction. In this situation, the rate of reaction decreases as the temperature is raised. Thus, the value of E_a can be

employed to evaluate the difficulty and the temperature dependent of interested dehydration reaction.