CHAPTER I

INTRODUCTION

Dissolution is an important characteristic in pharmaceutical solid dosage forms for dissolution is a primary step which solid substance dissolves into solution. Dissolution may indicate the potential availability of drug substances for absorption. The poor dissolution characteristic of relatively insoluble drugs has long been a problem to pharmaceutical industries. During 1989-1990 Medical Sciences Department, Thailand, reported that about 56 % of indomethacin and 24 % of piroxicam solid dosage forms manufactured by local manufacturers failed to meet the requirement of dissolution test. (Department of Medical Sciences, annual report 1989 and 1990) USP XXII requires that the dissolution of indomethacin must not less than 80 % (Q) dissolved in 20 minutes, and that of piroxicam must not less than 75 % (Q) dissolved in 45 minutes. This study aims to find the technique to solve the poor dissolution problem of indomethacin and piroxicam solid dosage forms by using β-cyclodextrin as an excipient. β-Cyclodextrin was used in drug formulations as either one of the followings: complexing agent, auxiliary additive, carrier, solubilizer and tabletting ingredient. Many techniques that are eutectic mixture, solid dispersions have been investigated in order to increase dissolution rate of the preparations. Some of these methods proved to be of limited use. Drugs that are unstable at or near their melting points and those that do not recrystallize from the melt are unable to use such methods. The solid dispersion technique has some processing problems such as the solid

dispersion powders tend to be wax like substances. Besides some of these techniques use an organic solvent or high temperature in the preparation. The volume of organic solvent used may be excessive and cause damaging to the environment. The degradation of the thermolabile drug substances may occur during the process. In addition the organic solvent may be deposit as residual solvent in the products. Tablets prepared by solid dispersion technique have superior dissolution, nevertheless when aging the dissolution might decrease. Therefore the purpose of this study is to find the appropriate method to increase the dissolution of indomethacin and piroxicam solid dosage forms by using β-cyclodextrin as an additive. The wet kneaded method between drugs and β-cyclodextrin was chosen according to its simplicity and easily adopted by local manufacturers. Factors affected the method such as the amount of solvent used, kneading time and temperature were thoroughly studied. In this study, β-cyclodextrin was chosen as an excipient because β-cyclodextrin had raised an interest in pharmaceutical technology, remarkably for its ability to form inclusion complex. In addition β-cyclodextrin is more readily available than other cyclodextrins because of its unique size, easy to be commercially obtained, non toxic and physiologically accepted. Wet kneading of drug and β-cyclodextrin could affect drug solubility concerning the inclusion complex formation or change in particle size of drug. Besides kneading process provides the system with good mixing of the system and makes drug surface becomes hydrophilic.

The objectives of this work were as follows

1. To study the effect of wet kneading of drugs with β-cyclodextrin on the aqueous solubility of indomethacin and piroxicam
2. To observe the dissolution of indomethacin capsules and piroxicam tablets when using the wet kneading process.
3. To compare the effects of β-cyclodextrin and sodium lauryl sulfate on enhancing the dissolution of indomethacin tablets and piroxicam capsules in the wet kneading method.

Literature Reviews

Methods used for enhancing the drug dissolution are based on the Noyes and Whitney equation

$$\frac{dc}{dt} = k \frac{DS}{vh} (C_s - C_t)$$

where dc/dt = the dissolution rate
k = dissolution rate constant
D = the diffusion coefficient
S = surface area
h = thickness of the diffusion film
v = volume of the dissolution medium
C_s = the solubility of the solute
C_t = the concentration of the solute.

Most methods recommended for improving the dissolution depend either on enhancing the solubility of drugs or increasing their effective surface area. (Hamed, 1989; Khan, 1981)

1. Increasing the Effective Surface Area of the Drug.

The reduction in particle size of poorly water soluble drug is the most popular practice for increasing the dissolution. The reduction can be achieved through a variety of micronization processes such as grinding, ball milling and air attrition. An incorporation of surface active agent is another approach to increase the effective surface area of drug. Surface active agents can enhance the wetting due to lowering interfacial tension between the solid surface of drug particles and solvent. Small amount of surface active agents can increase the wetting and penetration properties of the dissolution medium. A concentration of surface active agents employed usually below critical micelle concentration that is insufficient to cause any increase in solubility but can increase the drug surface area exposed to the medium. Hom and Miskel (1970) demonstrated that the dissolution rates of capsules of many insoluble drugs could be remarkably enhanced when formulating with nonionic surfactants. Newton, Rowley and Tornblom (1971) used 1 % w/w of sodium lauryl sulfate to increase the dissolution rate of hydrophobic drug, ethinamate capsules. Najib and Suleiman (1985) reported that the aqueous solubility of indomethacin can be increased by the use of surface active agents, sodium lauryl sulfate and polysorbate 80.

2. Alteration of the pH of the Surrounding Medium

Dissolution of the weak acid is inversely proportional to the hydrogen ion concentration. Javaid and Cadwallader (1972) showed that increasing the pH of the microenvironment of the drug by incorporating buffering agents in the formulation improved the dissolution rate of aspirin.

3. Solute-Solvent Complexation Reactions

Molecular complexation between solutes and solvents can affect the dissolution. Higuchi, Dayal and Pitman (1972) studied the dissolution of 2-naphthol tablets in cyclohexane (an inert solvent) containing various amounts of additives such as 1-propanol and 1-undecanol. These additives are known to react rapidly and reversibly with the dissolved molecules of 2-naphthol to yield soluble complexes. These major complexation mechanisms in this system are hydrogen bonding. A solute and a solvent that form a hydrate or a solvate lead to increase solubility.

4. Eutectic Mixture and Solid Solution Techniques

The use of binary system could improve solubility and dissolution of sparingly soluble drugs. This binary system consists of a water soluble compound acting as a carrier or host and drug acting as guest molecule. There are two mechanisms for enhancement the solubility and dissolution. The first one is related to particle size reduction in the eutectic-mixture formed by the poorly soluble drug and rapidly soluble carrier. The second one is the solubilization effect of the carrier. The systems involve randomized placement of drug molecule interspersed in the carrier either interstitial or by molecular replacement in the crystal lattice. When the eutectic mixtures exposed to the dissolution medium, the carriers dissolved rapidly leaving the insoluble drug in a state of microcrystalline dispersion consisting of extremely fine particles. Goldberg, Gibaldi and Kanig (1966) reported that the solubility and dissolution rate of griseofulvin were considerably improved by forming the eutectic mixture with succinic acid.

5. Dispersion Technique

Solid dispersion was defined as one or more active ingredients in an inert carrier. Drug molecules are distributed throughout a solid matrix by fusion or by solvent method. The selection of the carrier has an ultimate influence on dissolution characteristic of dispersed drug. Chiou and Riegelman (1969) recommended polyethylene glycol, a non toxic water soluble polymer, as an excellent universal carrier for improving dissolution rate of water insoluble drugs. Ford and Rubinstein (1978) and Corigan, et al. (1985) studied the solid dispersion of indomethacin-polyethylene glycol 6000 and indomethacin-polyvinylpyrrolidone respectively. They reported that dissolution illustrated the higher energy of indomethacin in these systems. Spray drying of indomethacin with up to 20 % polyvinyl-pyrrolidone gave amorphous solid.

6. Micelle Solubilization

Surface active agents are known to increase the solubility of drugs after reaching critical micelle concentration. A fairly large amount of surface active agents may need to be incorporated to increase solubility resulting from micelle solubilization leading to pharmacological toxicity. Therefore the use of micelle solubilization technique for improving the solubility of drugs was limited. The surfactant used should be proved to be almost pharmacological inert.

7. The Use of Metastable Polymorphs

Haleblian and McCrone (1969) reported the use of specific polymorphic form possessing the highest solubility as one of the technique that could be applied to increase the dissolution. Metastable polymorphic

crystalline forms can exert a great influence on the solubility. The new polymorphic forms can be synthesized through various recrystallization procedures from different organic solvents. Vrecer, Srcic and Smid-Kobar (1990) studied piroxicam polymorphisms by crystallization from a number of solvents and through melt cooling method.

8. Selective Adsorption on Insoluble Carriers

Wurster and Polli (1961) demonstrated that the use of suitable amount of an adsorbent could enhance the dissolution rate by maintaining the concentration gradient effect at its maximum. Monkhouse and Lach (1972) reported on the successful application of the surface adsorption technique for improving the dissolution of several poorly soluble drugs using various forms of silica. McGinity and Harris (1980) demonstrated the marked improvement in dissolution rate of indomethacin incorporating with colliodal magnesium aluminium silicate. The rapid release of drug from surface of clay was due to the weak physical bonding between the two materials.

9. Complexation with Cyclodextrins

Cyclodextrins can form an inclusion complex with smaller molecules. They are able to uptake various guest molecules into their central cavity. The size of guest molecules is a decisive criterion for the formation of stable inclusion complexes because guest molecules have to fit at least partly into the cavity of the cyclodextrins. The inclusion complex alters a variety of physicochemical properties of the drug molecules such as solubility, dissolution and stability. Drugs that are least

soluble in water often show the greatest proportional increase solubility in the presence of a given concentration of cyclodextrin.

Factors Affecting Dissolution and Bioavailability of Solid Dosage Forms.

There are several factors other than those related to physicochemical characteristics of active ingredients that may affect the dissolution and bioavailability of solid dosage forms. These factors generally are: Formulation factors, Processing factors and Storage factors

1 Formulation factors

Dissolution of pure drugs can be altered significantly when mixing with various adjuvants during manufacturing the dosage forms. These adjuvants include diluents, binders, disintegrants, granulating agents and lubricants. Diluents are found to potentiate dissolution of sparingly soluble drugs. Marlowe and Shangraw (1967) reported that the use of starch as a diluent was shown to produce sodium salicylate tablets with a much faster dissolution rate than when using lactose. Cyclodextrins are particularly useful adjuvants to form drug-adjuvants complexes to improve drug solubility. This will be an essential phenomenon in increasing therapeutic efficacy of drugs in application to manufacturing. Usually excipients used in solid dosage forms are inert but this is not the case of cyclodextrins, owing to their intrinsic reactivity characteristics. Lubricants usually form a water repellant coat around the granules. The retarding effect of this water repellant film was shown to be the most important factor in influencing the rate of dissolution of solid dosage forms.

2 Processing factors

Many processing methods used in the manufacture, including the wet granulation, greatly influenced dissolution rate of the active ingredients. Wet granulation was considered a superior method than dry granulation and double compression (Marlowe and Shangraw 1967). The compression force utilized in the tabletting process had quite an effect on the dissolution of the final products. The high compression force might inhibit wettability of the tablets due to the formation of a firmer or more effective sealing layer under high pressure.

3 Storage factors

The extent of the effects of storage on tablet dissolution rate was found to be largely formulation dependent. One of the prime factors found to influence the change in dissolution behavior of tablets on storage is the moisture content of the granules and the sensitivity to moisture of excipients utilized.

Indomethacin (Mathew, James and Edward, 1984)

The molecular structure of indomethacin is shown below. The empirical structure is $C_{19}H_{16}ClNO_4$ with molecular weight of 357.81

Indomethacin is an odorless, white to yellowish crystalline powder. It is known to exist polymorphism. It is a weak acid with the pk_a value of 4.5. Indomethacin has proved to have anti-inflammatory and pain relieving effect in gout and rheumatoid arthritis. It is stable in neutral and slightly acid, but decomposed by strong alkali. Indomethacin undergoes hydrolysis under alkaline condition to p-chlorobenzoic acid and 2-methyl-5-methoxy-indole-3-acetic acid. Strong sunlight induces an increase in color of indomethacin. Ionic or non ionic surfactants increase the stability of indomethacin (Krasowska 1978). Pathway of indomethacin hydrolysis was shown below. (Hajratwala and Dawson 1977; Cipiciani, et al. 1983) Solubility of indomethacin was summarized in Table 1.

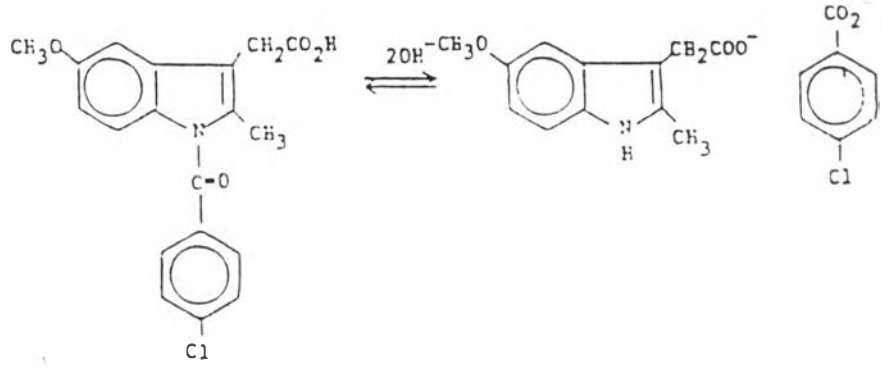


Table 1 Solubility of Indomethacin in Various Solvents.
(Matthew, et al. 1984)

Solvent	Temp(°C)	Solubility
Water	25	0.40 mg/100 ml[a]
Water	25	0.52 mg/100 ml[b]
Water	25	0.88 mg/100 ml[c]
Water	RT	Practically Insoluble
Phosphate Buffer pH 5.6	25	3 mg/100 ml[a]
Phosphate Buffer pH 5.6	25	5 mg/100 ml[b]

Table 1(cont.) Solubility of Indomethacin in Various Solvents. (Matthew, et al. 1984)

Solvent	Temp(°C)	Solubility
Phosphate Buffer pH 6.2	25	11 mg/100 ml[a]
Phosphate Buffer pH 6.2	25	16 mg/100 ml[b]
Phosphate Buffer pH 7.0	25	54 mg/100 ml[a]
Phosphate Buffer pH 7.0	25	80 mg/100 ml[b]
Ethyl alcohol (95 %)	RT	1 in 50
Chloroform	RT	1 in 30
Ether	RT	1 in 45
Methanol	25	32 mg/gm
Benzene	25	4 mg/gm
n-butanol	25	19 mg/gm
sec-butanol	25	27 mg/gm

[a]Form I, [b]Form II, [c]Form III

Polymorphic Forms of Indomethacin.

Indomethacin may exist in at least four polymorphic modifications (Matthew, et al. 1984, Borka 1974). Melting points of indomethacin polymorphic forms were shown in the Table 2

Piroxicam

The molecular structure of piroxicam is shown below. The empirical structure is $C_{15}H_{13}N_3O_4S$ with molecular weight of 331.35.

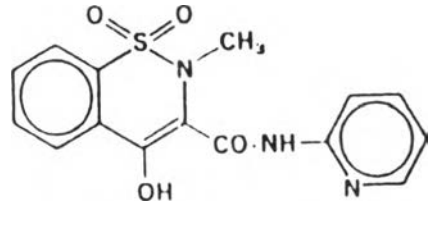
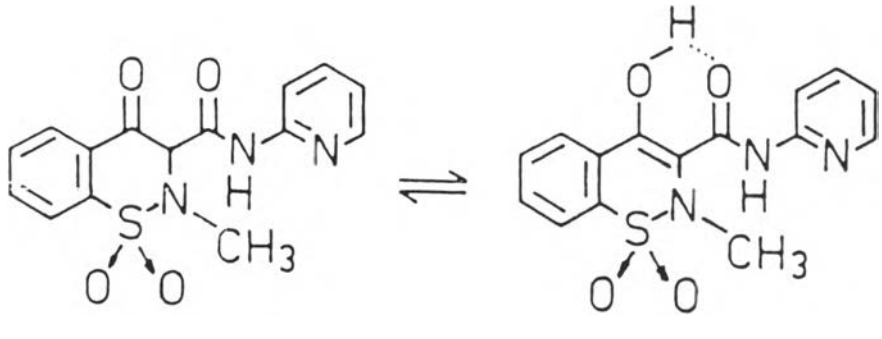


Table 2 Melting Points of Indomethacin Polymorphs

Form	Melting Point (°C)
Form I (type γ)	160-161.5
	160
	158
Form II (type α)	154.5-155.5
	154
	152
Form III	148
Form IV	134
Type β	158-160.5

Piroxicam is one of the most potent nonsteroid anti-inflammatory agents. Piroxicam is an odorless, colorless crystalline powder, poorly soluble in water, dilute acid and most organic solvents. Slightly soluble in alcohols and in aqueous alkaline solutions. pK_a are 5.1 and 1.8. The monohydrate form of piroxicam is slightly yellow. The change in color due to tautomerization.

Tautomerism of Piroxicam (Fini, et al. 1992)



Solubility of Piroxicam in Various Solvents (Mladen, et al. 1986)

1 g/10 ml Dimethylformamide

1 g/10 ml Dimethylsulfoxide

1 g/20 ml Chloroform

1 g/50 ml Acetone

Not Soluble in water and cyclohexane

Polymorphic Forms of Piroxicam

Piroxicam exists in four polymorphic forms and one pseudopolymorphic modification. (Vrecer, et al. 1991). Melting points of piroxicam were shown in Table 4

Table 3 Solubility of Piroxicam in Various Buffer Solutions (Herzfeldt and Kummel 1983)

pH	mg %
2.0	2.3
3.0	1.6
4.0	1.9
5.0	2.4
6.0	7.6
7.0	57
7.5	103

Table 4 Melting points of Piroxicam Polymorphs

Form	melting point (°C)
Form 1	201.6
Form 2	195.5
Form 3	178.4
Form 4	164.1

Cyclodextrins (Duchene and Wouessidjewe 1990; Duchene, et al. 1986; Saenger 1980; Szejtli, 1982; Stenphen, et al. 1984 and Strattan E Charles, 1990)

1. Structure and Properties of Cyclodextrins

Cyclodextrins are oligomers of glucose that are produced by enzymatic (Cyclodextrin transglycosylase, CTG) degradation of starch. Cyclodextrins are classified by the number of α-1, 4-linked glucose units that occur in their molecular structure. Alpha (α)-, Beta (β)-, and Gamma (γ)-cyclodextrin has six, seven, and eight glucose units, respectively. In these compounds, the C-1 chain conformation of the glucose monomers imparts to the molecule a cone-like structure in which the hydroxyl groups are oriented on the exterior of the torus. The narrower end of the cone contains primary hydroxyl functionality while the wider face contains the secondary hydroxyl groups. This arrangement makes the cyclodextrin exterior decidedly hydrophilic. The secondary hydroxyl groups can, however, interact via hydrogen bonding to stabilize the crystalline lattice. This reduces to a large extent the solubility of cyclodextrins, especially β-cyclodextrin in water. Most importantly, the interior of the cyclodextrin

cone is hydrophobic due to the presence of the skeletal carbons and ethereal oxygen that line the cavity. The result of this architecture is a lipoid microenvironment that can solubilize non-polar compounds.

Cyclodextrins are stable in alkaline solutions. They are susceptible to acid hydrolysis. Partial acid hydrolysis of cyclodextrins produces glucose and series of cyclic maltosaccharides. Stability of cyclodextrin toward acid hydrolysis depends on temperature and acidity. Under normal experimental condition, pH higher than 3.5 and temperature lower than 60 °C, β-cyclodextrin is fairly stable, non hygroscopic and as stable as sucrose or starch. They can be stored without deterioration. An aqueous cyclodextrin solution is not viscous. The approximate polarity of β-cyclodextrin in 100 mol per litre aqueous solution is similar to that of 40 % solution of alcohol in water. Taken as a whole, β-cyclodextrin is water soluble compound that can form reversible complex with smaller molecules that can fit into the hydrophobic cavity of cyclodextrin. The physicochemical properties of the drug molecules are changed. At the pharmaceutical level, the applications of inclusion complexes are essential in the improvement of molecular stability, solubility and bioavailability. Structure of β-cyclodextrin is shown in Fig 1 and characteristics of α, β, γ-cyclodextrins. are shown in Table 5.

2. Cyclodextrin Inclusion Complexes

Inclusion complex is a form of a chemical complex which one molecule is enclosed in another molecule. The cyclodextrin molecules act as 'hosts' into whose cavities foreign 'guest' molecules may totally or partially fit. The interaction between host and guest are

a) van de waals interaction between guest and host

b) ability of guest molecules of suitable size and shape to be physically accommodated in the cyclodextrin cavity.

Table 5 Characteristics of α, β, γ-Cyclodextrins

	Alpha (α)	Beta(β)	Gamma(γ)
Molecular weight	972	1135	1297
Glucose monomers	6	7	8
Internal cavity diameter (A°)	5	6	8
Water solubility(g/100 mL:25°C)	14.5	1.85	23.2
Surface tension (mN/m)	71	71	71
Melting range (°C)	255-260	255-265	240-245
Water of crystallization	10.2	13-15	8-18
Water in cavity	6	11	17

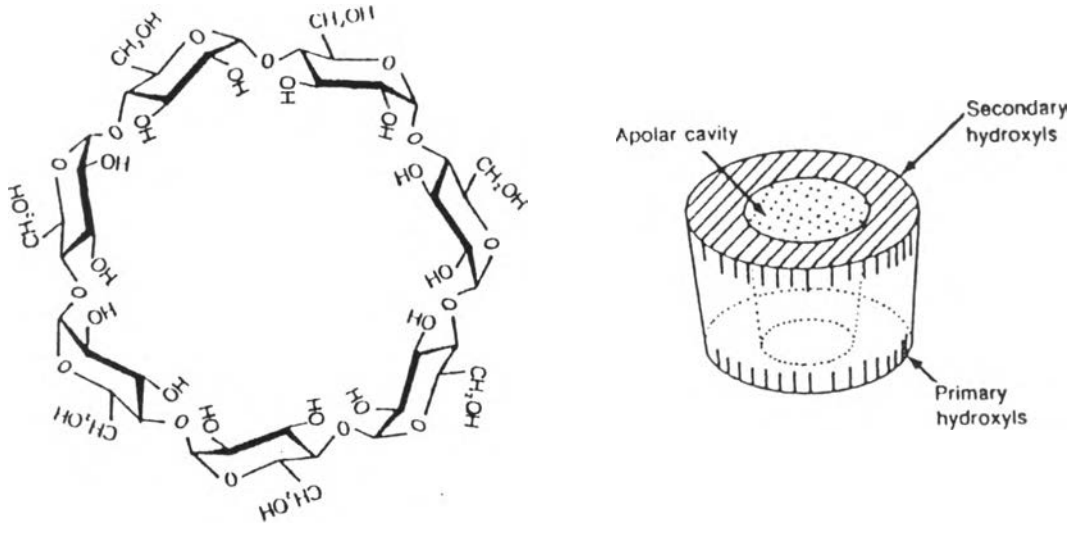


Fig 1. Structure of β-cyclodextrin

3. Preparation of Inclusion Complexes

Mechanism concerned in preparation of inclusion complex is the diffusion of drug molecules in contact with cyclodextrins needs at least one solvent (water, alcohol). In stirring medium several kinetic reactions may occur leading to the formation of inclusion complexes. In direction 1, at the end of the reaction, equilibrium is reached; it can be modified by varying the temperatures or solvent quantities.

Reaction mechanism of production of β-cyclodextrin inclusion compound is as follows (Serpelloni, 1990)

$$\begin{array}{lccccc} \text{Insolubles} & \text{CD} & & \text{A} & & \text{CD-A} \\ & 1 \downarrow\uparrow S_{CD} & & 1 \downarrow\uparrow S_A & & \downarrow\uparrow S_{CD\text{-}A} \\ \text{Solutes} & n\,\text{CD} & + & m\text{A} & \xrightarrow[K_C]{} & \text{CD-A} \end{array}$$

CD : Cyclodextrin molecule

A : Guest molecule

CD-A : Inclusion complex

n : number of CD molecule in the inclusion complex

m : number of A molecule in the inclusion complex

S_{CD} : solubility of cyclodextrin

S_A : solubility of guest A

$S_{CD\text{-}A}$: solubility of inclusion complex

The equilibrium between A and CD-A is characterized by the equilibrium constant (K_C)

$$K_C = \frac{CD\text{-}A.}{(CD)^n(A)^m}$$

4. Production of Cyclodextrin Inclusion Complexes

There are many methods for the production of inclusion complex which are :

4.1. Precipitation method

It is the most reliable method to isolate inclusion complex from saturated aqueous solution. Drug molecule is introduced under solid, liquid or gaseous form into the totally solubilized cyclodextrin. After a long mixing time, the blend is cooled in order to recover cyclodextrin-drug inclusion complex. The complex is separated by filtration or centrifugation. This method is not applicable to the system with an A-type solubility phase diagram because of the formation of a soluble inclusion complex. It is also unsuitable for a large scale because of the use of high volume of water and time consuming.

4.2. Kneading method

The drug substance is added to the cyclodextrin and water to form a slurry which undergoes an increase in viscosity with continue mixing. This may concentrate a paste which can be dried and powdered. Kneading method is advisable to use in industry because the method is rapid, simple, safe and inexpensive (Serpelloni and Mentink 1990). In comparison, the purity of the complexes prepared from kneading method are lower than those from the precipitation method.

4.3. Freeze-drying, Spray drying method

The drug is dissolved in water using ammonia solution if necessary. A required proportion of β-cyclodextrin is then dissolved in the

drug solution. The mixed solution is then freeze-dried or spray dried. The complexes obtained are amorphous structure. This method is suitable for water soluble guest. Lin, et al. (1989) prepared the inclusion complexes of indomethacin, piroxicam, acetaminophen and warfarin with β-cyclodextrin by using spray drying technique. The spray dried products had poor flowability and compressibility. However the dissolution rates of the drugs were faster than those of pure drugs and physical mixture of drugs and β-cyclodextrin. Kurozumi, et al. (1975) reported that the freeze drying method was useful to obtain the inclusion complexes of drugs with β-cyclodextrin if the aqueous solution of the drugs were prepared and then added a small amount of ammonia before freeze-drying.

4.4 Grinding method

Lin, Kao and Yang (1988) prepared paracetamol inclusion complex by grinding the mixture of paracetamol and β-cyclodextrin in a ceramic ball mill for 24 hours. An amorphous inclusion complex is formed. Nakai (1986) studied the ground mixture of aspirin with β-cyclodextrin by grinding in a vibratory mill, the result indicated that aspirin became amorphous in the ground mixture with β-cyclodextrin.

4.5 Sealed heating method

Sealed heating is a new method for preparing drug-β-cyclodextrin inclusion complex. The mixtures of drug and β-cyclodextrin were sealed in ampoule, then heated at a definite time and temperature in an oil bath. The drug was then included in β-cyclodextrin cavity. (Nakai, et al. 1987; 1989)

5 Method for Detection of Inclusion Complexes

5.1 Inclusion Complexes in Solution

The formation of inclusion complex in solution can be detected by various methods such as kinetics, thermodynamics, potentiometric and spectroscopic. When guest molecule is included in the cyclodextrin cavity, the absorption and fluorescence spectra usually change suggesting that the chromophore of the guest is transferred from aqueous atmosphere to cyclodextrin cavity. Potentiometric titration method is applicable to detect the inclusion complex formation in which the guest has acidic or basic functional group. By bonding to cyclodextrin, pk_a value of acidic guest is usually increased while that of the basic one is decreased. The great practical is to determine the solubility constants. A cyclodextrin inclusion complex in solution is always in kinetic or thermodynamic equilibrium. This equilibrium is described by solubility constant (K_c). The K_c value can be determined by phase solubility method.

5.2 Inclusion Complexes in Solid State

Drug-cyclodextrin inclusion complexes exist as static species with constant stoichiometry in the solid state that can be detected by physical methods.

5.2.1 Infra-red Spectrophotometer

Complex formation may be proved in some cases by infrared studies, but this method is of limited use. This is due to the spectra of cyclodextrins representing the majority of the complex being hardly influenced by complex formation. Some investigations showed the

chemical modification did occur during interaction of drug with cyclodextrin. (Nakai, et al. 1980)

5.2.2 X-ray Powder Diffraction

Since liquid guest molecules do not produce diffraction patterns, if the diffractogram differs significantly from that of uncomplexed cyclodextrin, the complex formation can be established. Thus, in the case of liquid guest molecules, X-ray powder diffraction is particularly useful. Powder X-ray diffractometry is a useful method for detection of β-cyclodextrin inclusion compounds in powder states. The diffraction pattern of the inclusion compound is clearly distinct from the superposition of each component if true inclusion compound exist.

5.2.3 Method Involving Heating

The thermo analytical system (TAS) involves the sample being heated in a sealed glass tube with a capillary outlet. This technique is a pyrolytic thin layer chromatography and found to be the most suitable technique for testing volatile oil inclusion complexes. Differential thermal analysis (DTA) can be appreciated due to the sensitivity of this technique. Any change in the crystalline state of a material will be detected. This lends itself very readily to detection of inclusion complex. Differential scanning calorimeter (DSC) is very similar to differential thermal analysis. Differential scanning calorimeter is currently used as a source of information in the study of solid state interaction of drugs with cyclodextrins. (Ford and Rubinstein 1981). The interpretation of the thermal effects recorded for the given drugs and cyclodextrins system is possible only when the thermal behavior of each component is known.

Differential scanning calorimeter analysis of β-cyclodextrin reveals thermal effects which can be attributed to not only the dehydration and melting with the decomposition of β-cyclodextrin but also solid-solid phase transitions.

6 Phase Solubility

The solubility method was described by Higuchi and Connors (1965). Phase solubility analysis is used to determine the relationship between the total concentration of dissolved drug and the concentration of added cyclodextrin. The solubility method is based on monitoring changes in solubility of drug by the addition of β-cyclodextrin. Excess amount of the drug was added to a solution of β-cyclodextrin in various concentrations, shaken at a constant temperature. After equilibrium is attained, the solution phase is analyzed for total concentration of the drug in the solution. Changes in solubility of the drug are plotted as a function of β-cyclodextrin concentration. According to the definitions provided by Higuchi and Conners (1965), the two main types of solubility profiles are A and B. A-type curves indicate the formation of soluble inclusion complexes while B-type relationships indicate the formation of complexes with limited solubility. Each type is further subdivided. If a plot of cyclodextrin concentration versus the concentration of drug solubilized is linear, an A_L-type system is obtained. Positive or negative deviations from linearity give A_p- and A_n-type responses, respectively. A_p-systems generally reflect high order complexation at higher cyclodextrin concentrations meaning that more than one cyclodextrin molecule is complexing with the guest. If a complex of a drug and cyclodextrin is not soluble, a B-type curve is generated. Complexes of limited solubility give

B_S type relationships. For A and B_S-type systems, the initial linear portion of the curve can be useful in examining the efficiency of complexation. At point A solubility of the inclusion complex reaches its limit. The S_t (apparent solubility) of the guest is constant between A and B. After point B, where all the solid guest had been consumed, the guest in the solution is converted to the solid inclusion complex by further addition of β-cyclodextrin. The solubility constant (K_c) of 1:1 can be calculated from the slope and intercept of the initial straight line portion of the diagram from the following equation.

$$K_{1:1} = \frac{\text{Slope}}{S_0(1\text{-slope})}$$

S_0 refers to the solubility of the drug in the absence of β-cyclodextrin. The slope value is obtained from phase-solubility analysis.

The stepper the slope, the better the complexation. Szejtli (1981) evaluated the effect of β-cyclodextrin on the bioavailability of drugs and pointed out that the ideal stability constant should be between 100-1000 M^{-1} Smaller stability constants give too weak an interaction to improve the solubility whereas larger values hinder the absorption process. The schematic representation of phase solubility diagram was shown in Fig. 2

7 Cyclodextrin in Pharmaceutical Sciences (Duchene, et al. 1986; 1990; Jones, S.P., et al. 1984; Nambu, et al. 1978, Szejtli, 1982; Zecchi, V. et al. 1988)

The pharmaceutical applications of cyclodextrins are as follows

7.1 In the formulation of oral drug.

- Liquid compounds can be transformed into crystalline form which is then suitable for tablet manufacturing

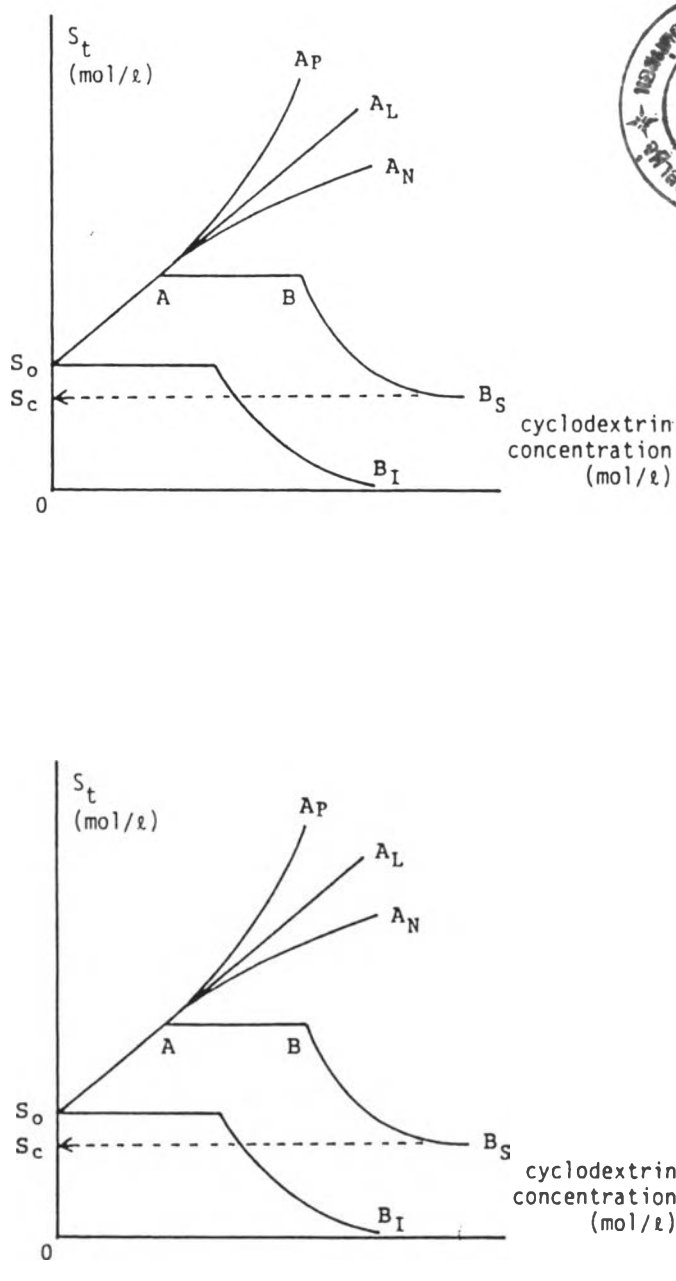


Fig 2 Phase Solubility Diagrams

A A-type diagram

B B-type diagram

- Masking an unpleasant taste or odor of compound

- Avoidance of an incompatibility of uncomplexed compound with other drugs or excipients in the formulation.

- Content uniformity of low-dose tablets is improved by making tablet of the microcrystalline complexes.

- Cyclodextrins and their complexes generally are not hygroscopic and they can be pressed to tablets of rather good mechanical properties.

7.2 Improvement of physical and chemical stability :

- Volatile compounds can be stabilized against loss by evaporation.

- Cyclodextrin inclusion complex protects oxidizable compounds against oxidation by air.

- Rate of decomposition, polymerization, autocatalytic reactions are considerably decreased.

7.3 Bioavailability of poorly soluble drugs can be enhanced :

- Solubility in water as well as the rate of dissolution of poorly soluble substances can be increased.

- The complexes are hydrophilic, easily wettable and readily soluble.

- Higher blood levels of poorly water soluble drugs can be achieved after the oral administration if they are complexed with cyclodextrin (possibility for reduction of doses).

- Reducing the hydrophobicity of drugs by cyclodextrin complexation improves their percutaneous or rectal absorption.

8. Toxicity of Cyclodextrins (Gergly, et al. 1982; Saenger, 1980)

After oral administration, cyclodextrins are not hydrolyzed during their transit through small intestine, hydrolysis occurs in colon. β-cyclodextrins are resistant to β-amylase, but they can be hydrolyzed by α-amylases. β-Cyclodextrin is poorly absorbed by small intestine. The oral administration of cyclodextrin was not result in acute toxicity. No significant change in organs were observed in long term administration. LD_{50} of β-cyclodextrin is more than 12.5 g/kg in mice, 18.8 g/kg in rats, and 5 g/kg in dogs.

9. Reviews the Application of β-Cyclodextrin in Pharmaceutical Sciences

Hamada, et al. (1975) studied the interactions of α-cyclodextrin and β-cyclodextrin with several non-steroidal antiinflammatory drugs (indomethacin, flufenamic acid, mefenamic acid and phenylbutazone), comparing with glucose. The solubility of all drugs was found to increased with the addition of β-cyclodextrin while not with glucose. Szejtli, et al. (1982) found a 2:1 complex of β-cyclodextrin : indomethacin that helped to relieve the side effects of indomethacin (mainly gastric irritation) but a 1:1 complex however aggravated the side effects. Backenfeld et al. (1990) and Hamada, et al. (1975) reported that the p-chloro benzoic acid functional group of the indomethacin molecule was included into the cavity of β-cyclodextrin but the indole part of indomethacin was too large for inclusion. α-Cyclodextrin accelerated the hydrolysis of indomethacin because ring size of α-cyclodextrin might not be able to include the reactivity group of indomethacin into its cavity. β-Cyclodextrin includes the acid functional groups of the indomethacin

molecule within the cavity, thus improving the stability of indomethacin. Lin and Kao (1989) studied indomethacin, piroxicam, paracetamol and warfarin forming inclusion complex with β-cyclodextrin by spray-drying method and reported that the amorphous small particles were formed and led to increase dissolution. Nambu, et al. (1978) prepared freeze-dried inclusion complexes of β-cyclodextrin with nonsteroid anti-inflammatory drugs; which were flufenamic acid, ibuprofen, ketoprofen and indomethacin. They found the complexes with β-cyclodextrin had better dissolution characteristic compared to the complexes with the water soluble synthetic polymer, polyvinylpyrrolidone and polyethylene glycol. The drug β-cyclodextrin complexes are lower hygroscopicity and higher fluidity. The solubilization of sparingly soluble drugs by cyclodextrins was studied including sulfonamides, chloramphenicol, prostaglandin E_2, steroid hormones, naproxen, and phenyltoin. For rational design of drug formulations, cyclodextrin can be used as an active excipient. The possibility of using β-cyclodextrin as a filler has been reported by La Manna, et al. (1990). Szabo, et al. (1989) reported a significantly increase in dissolution of chloramphenicol was found by physical mixture of chloramphenicol and β-cyclodextrin. The improvement of dissolution of the physical mixtures was attributed to the combined effects of the hydrophilic properties of β-cyclodextrin and fragmentation of chloramphenicol crystals. Simple physical mixture of drug with β-cyclodextrin displayed better solubility than each drug itself. Shangraw, et al. (1990) studied dissolution of tablets made by wet granulation of both physical mixture and inclusion complex of progesterone and β-cyclodextrin. They found that dissolutions of all formulations containing β-cyclodextrin were much faster than those with microcrystalline cellulose.

Luu, et al. (1987) reported the enhancement of pharmaceutical activity of Cerm 3276 when grinding with β-cyclodextrin although no inclusion was formed. In tablet manufacturing, cyclodextrin can be used as an auxiliary substance (disintegrant, binder or diluent). Shangraw, et al. (1990) reported that the compatibility of tablet using cyclodextrin as a filler was excellent but the fluidity was insufficient for routine compression. Formulation containing β-cyclodextrin exhibited much faster and higher dissolution. The use of cyclodextrin showed considerable promise and needed to be explored further.