CHAPTER I

GENERAL BACKGOUND

Introduction

The dissolution rates of solid drugs are extremely important for the quality control of solid pharmaceuticals. It is important to determine potential availability of drug substances for absorption through dissolution, especially hydrophobic drugs. Dissolution of many hydrophobic drugs with extremely low aqueous solubility must be enhanced for potentially improving absorption and hopefully the bioavailability of the drug.

Spray drying technique offers significant versality over other means of drying. This process is the direct formation of solid particulates from droplets undergoing chemical reaction and particle size reduction during drying. It offers a one-step process which combine synthesis or chemical reaction, drying and agglomeration process. The dissolution rate of spray dried products might be attributed to the decreased in particle size and the formation of high-energetic amorphous state (Lin and Kao, 1989).

Cyclodextrins are used in the enhancement of the solubility of poorly water soluble drugs. Owing to their hydrophobic interior, the various cyclodextrins are capable of including a variety of hydrophobic solutes within the inner cavity. In the other way, they have been used to stabilize many drug substances that are unstable in the presence of air, light or heat. In some cases, they can stabilize drug substances that are susceptible to hydrolysis or oxidation by including them into their molecular cavities (Duchene and Wouessidjewe, 1990).

Indomethacin is a nonsteroidal antiinflammatory drug which is poorly water-soluble. It undergoes pH-dependent hydrolysis in aqueous solutions. Lin and Kao (1989) used beta cyclodextrin to improve the solubility of indomethacin by a spray drying technique. They found that the spray drying technique could be used to prepare the amorphous state of drug with beta cyclodextrin. The flowability and compressibility of the spray dried products were poor, due to the small particle size formed by the spray

drying process. However, the dissolution rates of drugs from tablets prepared by spray dried products was faster than pure drug and its physical mixtures.

Lin et al., (1991) continue to study the effect of different methods (kneading, spray drying and neutralization followed by freeze drying) on the physicochemical properties of IMC with both beta cyclodextrin and hydroxypropyl beta cyclodextrin. They found that the characteristic of the end products depended on the method of preparation. However, the end products prepared by the above methods may be great of value as rapidly dissolving indomethacin in water were formed.

Backensfeld et, al. (1990) studied the effect of various cyclodextrins (alpha, beta and gamma) cyclodextrin and hydroxypropyl beta cyclodextrin on indomethacin stability in phosphate buffer pH 7.4. They found that the most favorable ring size for the stabilization of indomethacin was the beta cyclodextrin.

Hamada et, al. (1975) investigated the interaction of indomethacin with beta cyclodextrin (prepared by recrystallization from water) and found that beta cyclodextrin stabilized the drug in aqueous solution and increased the solubility of indomethacin.

Sodium lauryl sulfate is an anionic surfactant used in the enhancement of the dissolution rate of poorly water-soluble drugs by the formation of micelles. Otsuka and Matsuda (1995) investigated the physicochemical properties of phenytoin combined with various kinds of surfactants (sodium lauryl sulfate, sodium deoxycholate and the sucrose ester of stearic acid) at 40% w/w by a cogrinding method. They found that all products ground with surfactants dissolved rapidly and gave constant drug concentrations after 10 minutes and during drug dissolution for 6 hours. Since the wettability of all ground products was improved by adding of surfactants, the initial dissolution of all ground products was very rapid. Cipiciani et al., (1985) studied the micellar effects on the basic hydrolysis of indomethacin. They found that anionic micelle inhibited the decomposition of indomethacin, whereas cationic micelles enhance the decomposition of indomethacin.

In order to improve the dissolution rate of indomethacin, the use of beta cyclodextrin and sodium lauryl sulfate in phosphate buffer pH 7.4 for spray drying process were studied. The spray drying conditions such as inlet air temperature and feed rate, where other publications have not yet done, were investigated. The physicochemical properties were also evaluated. The solubility and dissolution of drug prepared by the above spray drying conditions and different amount of beta cyclodextrin and sodium lauryl sulfate were eventually studied.

Objectives of the study

1. To study the effects of beta cyclodextrin and sodium lauryl sulfate including its compositions on the dissolution rate enhancement and other physicochemical properties of indomethacin by spray drying.
2. To study the effects of spray drying process and their conditions, such as inlet air temperatures and feed rates, on the dissolution rates and the physicochemical properties of indomethacin obtained with various compositions beta cyclodextrin or sodium lauryl sulfate.

Literature Review

Dissolution indicates the process by which a solid substance dissolves. This process is controlled by the affinity between the solid and the medium (Gennaro et, al., 1989).

The dissolution process of solids in liquids involves three steps:

(1) The removal of a molecule from the solute;

(2) Creation of a hole in the solvent; and

(3) Insertion of the solute molecule into the solvent (i.e. solute-solvent interaction). This interaction between the solute and the solvent is obviously dependent on the physical and chemical nature of the two participating molecules (Mosharraf et al., 1999).

There are many factors influencing in the dissolution rate of drugs including solubility, particle size and crystalline state. The other physical properties such as density, viscosity and wettability contribute to the general dissolution problems of flocculation, flotation and agglomeration (Gennaro et, al., 1989).

Solubility of a solid expresses as the concentration of the dissolved solid in the solvent medium, which becomes saturated solution and which is in equilibrium with the solid at a defined temperature and pressure. The solubility of a drug substance depends on the physical form of solid, the nature and composition of the solvent medium, the temperature and the pressure (Grant and Brittain, 1995).

Solubilities may be expressed in any appropriate units of concentration. The most convenient expressions of concentration are listed and examplified in Table 1.

The reduction of particle size of drug improves the drug solubility hence enhancing the dissolution rate. One of the methods recommended for particle size reduction is the formation of solid solution or molecular dispersion where the molecules

Table 1 Expressions for Concentration and Solubility

Symbol	Physical Quantity	Example
M_2	Molecular weight of the solute	M_2 = 300 g/mol
W_2	Weight of the solute	W_2 = 1.0 g
M_1	Molecular weight of the solvent	M_1 = 100 g/mol
W_1	Weight of the solvent	W_1 = 20 g
V_t	Volume of the solvent	V_t = 25 ml
ρ_t	Density of the solvent	ρ_t = 0.8 g/ml
ρ	Density of the solution	ρ = 0.9 g/ml

Concentration Units	And Expressions	Calculated from above
A (g/100 g solvent)	$= 100\ W_2/W_1$	A = 5.00 g/100 g
B (g/100 ml solvent)	$= \frac{A\rho_1}{100\ W_2/v_1}$	B = 4.00 g/100 ml
D(g/100 g solution % w/w)	$= \frac{100\ A}{100 + A}$	D = 4.76 g/100 g
E(g/100 ml solution % w/v)	$= D\rho$	E = 4.29 g/100 ml
m (mole/kg solvent = molarity)	$= 10A/M_2$	m = 0.167 mol/kg
c (mole/L solution = molarity)	$= 10E/M_2$	c = 0.145 mol/L
x (mole fraction)	$= \frac{W_2/M_2}{(W_1/M_1)+(W_2/M_2)}$	x = 0.0164

Source: From J. Jacques, A. Collet, and S. H. Wilen, *Enantiomer, Racemates, and Resolutions*, Wiley, New York, 1981, p. 168.

of the sparingly soluble drug are either dispersed interstitially in a water-soluble drug or replaced in its crystal lacttice (Gennaro et, al., 1989).

Disruption of the physical order of the molecules of a material which is initially well ordered structurally (i.e. purely crystalline) is a result of mechanical or chemical activation such as those listed in Table 2. These changes will affect the chemical or physical reactivity and thus the dissolution characteristics of the material (Grant and Brittain,1995). Materials which are changed to amorphous state are often metastable. They might convert to crystalline state when there are favorable condition such as elevated temperature or humidity. Absorbed moisture can act as a plastisizer to cause increased molecular mobility. The subsequent results could be recrystallisation or deactivation (Ahlneck and Zografi, 1990).

There are many approaches for improvement of solubility of poorly water soluble drugs such as salt formation, solubilization by molecular complexes, utilization of surfactants, cosolvent or cyclodextrins for enhancement of the solubility of drugs. This section reviews some useful approaches as following:

Salt formation is one of the most common approaches used to increase the solubility and dissolution rate of drug. The pharmaceutical literature contains many examples showing how salt formation can be used to increase the solubility of drug substances. For example, the solubility of nicardipine hydrochloride was found to be greatly affected by the nature of the carboxylate buffer system in which it was dissolved. The degree of solubilization was found to increase with the length of the alkyl chain, although solubility limitation within the various buffer systems limited the scope of the study. For example, the solubility of drug in water, 5.0 M acetate, 5.0 M proprionate, 1.5 butyrate and 1.0 M valerate are 5.1, 69, 270, 32 and 5.0 mg/ml (Grant and Brittain, 1995).

The solubilization of poorly water by surfactants has been used in pharmaceutical application due to both hydrophilic and hydrophobic structures of substances. The ability of a micelle to solubilized the limited aqueous solubility compounds can be explained from the consideration in Figure 1. Above the critical micelle concentration , these molecules orient themselves with the polar ends in

Table 2 Properties of the crystals or particles that may be modified by the processing stresses that are imposed during the manufacture of solid dosage forms.

Crystal properties	Processing stresses	Manufacturing procedures
Crystal structure	Temperature	Crystallization
Polymorphism	Pressure	Precipitation
Crystal solvation (solvates)	Mechanical	Milling
Crystal habit (shape)	Radiation	Mixing
Crystallinity (crystal	Exposure to liquids	Drying
defects)	Exposure to gases	Granulation
Crystal surface constitution	and vapors	Compressing
(polarity, irregularity,		Coating
wettability)		Storage
Expansivity, compressibility,		Transport
viscoelasticity, elasticity,		Handling
plasticity, hardness		
Particle size (distribution)		

Source : From P. York, *Int. J. Pharm.*, 14, 1 (1983)

interfacing with the aqueous solution and the nonpolar ends at the interior. A hydrophobic core is formed at the interior of the micelle, and hydrophobic solute molecules enter and occupy this region (Grant and Brittain, 1995).

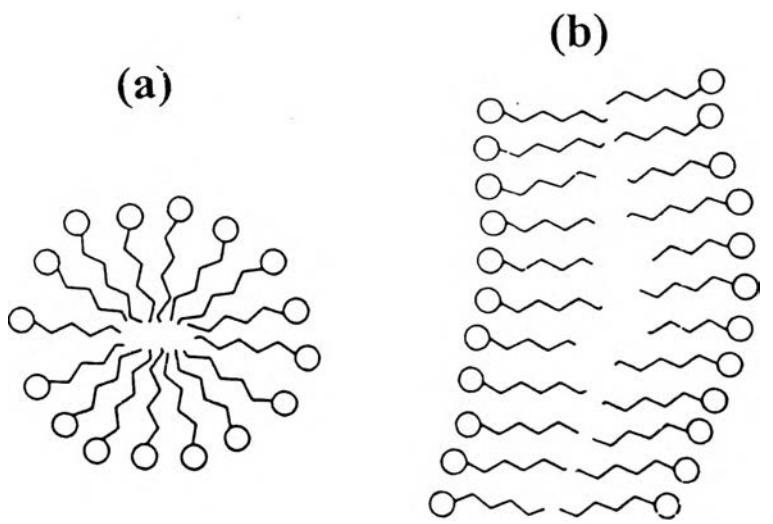


Figure 1 *Cross section of (a) spherical and cylindrical micelles, and (b) cylindrical and lamellar vesicles in aqueous solution. Each surfactant molecule making up the structure has a polar head-groups, depicted as a circle, and a nonpolar, hydrophobic chain, depicted as a zigzag.*

Cyclodextrins are used to solubilize of many drugs due to their hydrophobic interior. The number of studies describing the solubilization of drug compounds by cyclodextrins is extraordinarily large and has been summarized in the later.

Spray drying technique

Spray drying has been used extensively in the pharmaceutical industry, primarily in the production of raw drug materials such as antibiotics, and excipients, such as spray dried lactose. The pharmaceutical applications include granulation and microencapsulation processes" (Broadhead et al., 1992). Some studies use spray drying technique to improve the dissolution of drug by incorporation with cyclodextrins (Lin and Kao, 1989). In the other cases there have been an increasing interests on the development of novel delivery systems for protein and peptide drugs which focused its attention on spray drying as a means of processing these thermolabile materials. The potential utilization of spray drying in protein formulations for the lies in its ability to produce particles of controlled size and shape. This is critical development of dry powders suitable for inhalation and microparticulates for controlled drug delivery (Bodmeier and Chen, 1988).

The General Principles of Spray Drying

Spray drying is a process describing the transformation of liquid feeds into a dried particulate form by spray drying the feed into a hot drying gaseous medium (Master,1985). It is a one-step, continuous particle processing operation involving drying. The feed can either be solution, suspension or paste. The resulting dried product forms to powder, granules or agglomerates. The form of which depends upon the physical and chemical properties of the feed and the dryers design and operation (Master , 1979).

The Design and Operation of Spray Dryers

The spray drying process encompasses the following four stages (Masters , 1985):

(i) Atomization of the feed into a spray

(ii) Spray–air contact

(iii) Drying of the spray

(iv) Separation of the dried product from the drying gas

Atomization may be classified according to the nozzle design as rotary a atomization or two–fluid (pneumatic) atomization. In rotary atomization, the feed fluid is introduced into the drying chamber by means of a spinning disc or wheel which creates a spray of droplets. Pressure atomization occurs when the feed is fed to the nozzle under pressure which causes the fluid to be dispersed into droplets as it leaves the nozzle. The two–fluid nozzle separate the feed fluid and atomizing air into two lines that finally mix and the air causes the feed to break up into a spray.

Spray dryers may be designed to operate in a co-current manner, where spray and drying air pass through the dryer in the same direction or in a counter-current manner where the spray and drying air enter the drying chamber at the opposite ends. Co-current operation is preferable for the drying of heat sensitive materials since the dry product is in contact with only the coolest air. Also, the high rates of moisture evaporation enable the temperature of the dry product to be considerably lower than that of the air leaving the drying chamber. Counter-current drying, on the other hand, is a superior process in terms of heat utilization and economics, but subjects the driest powder to the hottest air stream.

The final step involves the separation of the product from the air stream. This is usually accomplished by means of a cyclone separator through which the air and product pass after exiting the drying chamber. Many dryers also allow for product collection at the base of the drying chamber.

There are numerous different spray dryer designs. Spray dryers systems are usually open cycle whereby the drying gas is discharged after use. In this manner, the drying gas would usually be air. In addition, the closed cycle spray dryers are available which enable organic solvents to be used as the feed medium. The closed cycle may be required if the material being dried is extremely susceptible to oxidation or has explosive tendencies (Takeuchi and Kawashima, 1987). Nevertheless, this system will get rid of the unacceptable solvents that create serious pollution problems using a high condenser to secure maximum recovery of the solvent, make closed cycle dryer more expensive than the open system (Nelson , 1982).

Advantages and Disadvantages of Spray Drying

Advantages (Master, 1979; Nielson, 1982)

1. Continuous in operation
2. Adaptable to full atomization
3. Dried product specifications are met through dryer design and operational flexibility
   (i) Required product form (particles as spheres, fines, agglomerates)
   (ii) Required product properties (dusty or dustiness, degree of flowability, wettability)
4. Applicable to both heat sensitive and heat resistant materials.
5. Economic in operation. Dried product specifications are related to properties of;
   (a) Particle size distribution
   (b) Appearance
   (c) Flowability
   (d) Color, cream, taste
   (e) Acidity
   (f) Sterility
6. Many kinds of feed stocks (solution, slurry, thixotropic paste or melted form) can be handled, if pumpable.
7. Corrosion and abrasion can be reduced or prevented because the material does not contact the equipment surface until it is dry.
8. Low maintainance costs
9. Low labor costs because only one operator is required, even large installation. The evaporation usually done under slight vacuum, this is easy to keep clean.
10. Some operation for both small and large dryers.
11. Spray drying is an airborne process, hence there is very low material hold up in the equipment.
12. Designs are available to handle
    (i) organic solvent explosion and fire risks
    (ii) explosive mixtures in air from powders
    (iii) odor products

(iv) toxic products

(v) products requiring aseptic and hygienic drying conditions.

Disadvantages (Broadhead et al., 1992)

1. High cost both in equipment and operation
2. Poor thermal effectiveness when extremely high drying temperature is used and cause heat degradation
3. High cost of the end product. Although, the expense of the process must be balanced against the advantages to be gained by using spray drying instead of an alternative processing strategy.

The Properties of Spray Dried Powders

Spray dried powders are approximately spherical with a narrow size distribution and are usually hollow. The hollow nature imparts a low bulk density to the powders, but despite this, their spherical shape mainly they are usually free flowing (Broadhead et al., 1992). By modifying the spray drying process, it is possible to alter and control the following properties of spray dried powders; appearance, particle size and size distribution, bulk density, particle density, porosity, moisture content, flowability, stability, dispersability, friability and retention of activity aroma and flavor (Masters, 1985).

An increase in the energy available for atomization (i.e. rotary atomizer speed, nozzle pressure, or air–liquid flow ratio in a pneumatic atomizer) will reduce particle size (Masters, 1979). Particle is usually increased as the feed concentration or viscosity increases (Masters, 1979). The rotation speed of the atomizer is the main factor affecting the drug content of the products. With increasing rotating speed, the drug content increases. The excipient is separated easily from the spray drying droplet than the drug because of the different density, which results in increasing the drug content in the product (Kawashima et al., 1983).

Masters (1979) described that at low feed rates, the droplet size is a high homogeneity. At high feed rates, the atomizing air cannot penetrate the thick liquid jets. Atomizing is incomplete and wide droplet-size distribution in the spray results.

According to Seagh (1977), increasing feed rates will lead to a reduction in the outlet temperature and increases in equilibrium solvent or moisture level.

The feed concentration or viscosity at the processing temperature influenced by the solid content of the feed. The yield can be increased by using a high total solid content (Broadhead et al., 1994). Masters (1979) reported that surface tension has minimal effect of particle size with an increase in feed surface tension and density as well as with concentration and viscosity. If the feed rate is increased, particle will again increase.

The effect on particle size appears to be highly dependent on the material being dried (Crosby and Marshall, 1985). A tendency for the particle size to increase and agglomerate with increasing inlet temperature is observed by Broadhead et al. (1994). A high inlet temperature gives rise to products which are larger and have lower moisture content. The effect of temperature on drug content is presented by Kawashima (1984). With decreasing with temperature, the drug content increases. The effect of temperature on decreasing drug content is more significant than that of atomizing rotation speed.

An increased inlet temperature often caused a reduction in bulk density, as evaporation rates are faster, a product dries to a more porous or fragmented structure. It also showed great effect in reducing the particle size (Masters, 1979). In contrast, Newton (1966) reports a study where the particle size of some materials was shown to increase as the drying air temperature increases.

The outlet temperature of the spray dryer is the single most important parameter that determined the water drying rate and moisture content of the product (Maa et al., 1988, Masters, 1979). It was determined solely by the main effects of the inlet air temperature and the solution feed rate. At a given inlet temperature, a decrease in feed rate will cause the outlet temperature to rise and resulting in a lower moisture content of the final product.

The Application of Spray Drying for Dissolution Rate Improvement

Spray drying is a convenient method for the production of pharmaceutical complexes, since solid particulates can be produced from droplet undergoing chemical reaction in one step.

The application of spray drying to alter the biopharmaceutical properties of individual drugs has been studied, given the influence drug solid state properties may have on bioavailability. Specially, drug particle size, degree of crystallinity and polymorphic form may frequently alter drug dissolution and hence bioavailability. Sodium salicylate (Kawashima,Matsuda and Tekenaka, 1972), phenobarbitone and hydroflumethiazole (Corrigan, Sabra and Holohan , 1983) when spray dried with excipeints resulted in alteration of the crystal form of the drug, either to a different polymorphic form or to an amorphous phase.

Takeuchi and Kawashima (1987) used spray drying to prepare spherical particles loaded with fine drug crystals (tolbutamide). A much greater drug to core ratio was achieved compared to a conventional ordered mix or solvent deposition system. It was found that when efficient disintegrating agents were used as the core material, the particles had good dissolution properties despite the high drug loading.

The solubility of non-steroidal anti–inflammatory drugs can be substantially improved by spray drying, due to an alteration in the predominant polymorphic form. Indomethacin, which had a melting point of around 160 °C (the exact value depending on the polymorph in question) was spray dried as an alcoholic solution in the presence and absence of polyvinyl pyrolidone (PVC) (Corrigan, Sabra and Holohan,1985). In the absence of PVC, a glassy amorphous phase formed on the wall of the cyclone separator which became within a week. In the presence of PVP an amorphous phase was still formed but the conversion to a crystalline phase was significantly retarded. When the PVP concentration was increased above 20% an amorphous powder formed in the collecting vessel. A physical stable amorphous form of the drug was considered desirable because of its greater solubility. Ketoprofen and ibuprofen could also be converted to stable amorphous solid products when spray dried in the presence of 50 – 75% PVP. These drugs have an increased PVP requirement due to their lower melting points. In the absence of PVP the products were liquids.

The same authors investigated the effect of spray drying on various thiazide diuretics. When hydroflumethiazide was spray dried from an alcoholic system containing 20% PVP, the solubility was increased to 4-5 times that of the corresponding physical mixture. This compared with a solubility increased by a factor of only 1.6 when pure drug was spray dried, even though the pure spray dried drug was amorphous. Also, when pure drug was spray dried, it converted to a crystalline form within about 12 days. Spray drying in the presence of 10% PVP resulted in the solubility about 2.5 times that of the crystalline drug. The authors therefore proposed the existence of two amorphous state, with the pure drug amorphous phase still having considerable structure despite the absence of crystallinity. The degree of disorder was proposed to increase with increasing PVP content as evidenced by thermodynamic studies (Corrigan et al.,1983).

Inclusion complexes of various drugs, such as paracetamol, with beta cyclodextrin were prepared by spray drying (Lin and Kao, 1989). The drug–beta cyclodextrin complexes existed in the amorphous state, with a mean particle size of less than 10 μm and a range of 3-40 μm. In all cases the particle size of the complex was smaller than that of the original drugs, and the particles were found to be approximately spherical. However, the powders were found to have flow properties and also to exhibit poor compressibility. The dissolution rate of tablets formulated from the spray dried complexes was greater than from tablets formulated from physical mixtures. This was attributed to a decrease in drug crystallinity, small particle size and complex formation.

Spray drying salicylic acid with acacia increased the drug solubility and dissolution rate. This was partly due to a decrease in drug crystallinity. Formulations with low weight ratios of salicylic acid to acacia appeared to be amorphous, however an increase in the ratio of salicylic acid to acacia led to increase in the crystallinity of the product. If the ratio is increased above a certain point, the salicylic acid is not completely encased, and thus may sublime and recrystallize in the collector which would result in an apparent increase in crystallinity of the spray dried product. The authors concluded that although spray drying did reduce drug crystallinity, it was the greatly improved wettability of the product due to the incorporation of the acacia that was mainly responsible for the improved solubility.

Kawashima et al. (1983) observed that the temperature at which spray drying is carried out can have a significant effect on the predominant crystal form of a drug. In preparing a pyrabarbital complex has greater degree of amorphous when the feed was dried at a temperature of 145 °C as opposed to 85 °C. This was attributed to the more rapid evaporation which occurs at higher temperatures.

The production of beta cyclodextrin complexes by spray drying was evaluated as a potential method for increasing the bioavailability of the poorly soluble, hydrophobic drug, diazepam (Bootsma et al., 1989). Differential scanning calorimetry (DSC) data indicated that at levels of 5% diazepam at higher drug loading, pure diazepam was also present. Diazepam was also spray dried with lactose, with which at cannot complex, in order to as certain the relative importance of complexation in the observed bioavailability increase. It was noted that all spray dried formulations dissolved much faster than drug/excipient physical mixtures. The authors found that at low drug levels complexation played only a minor role in the dissolution rate increase, since spray drying lactose was equally effective. This led the conclusion that the formulation of intimate physical mixtures by spray drying with the highly soluble excipients was largely responsible for the improved dissolution profiles. However at high drug levels, beta cyclodextrin formulations had a considerably higher intrinsic dissolution rate than lactose formulations. Data obtained under conditions where the immediate microenvironment of the formation were relatively undisturbed (such as *in vitro* data obtained at slow stirring rates) show enhanced dissolution from beta cyclodextrin formulations even when the drug was present at low concentrations. This was attributed to the cyclodextrin increasing the diazepam solubility in the boundary layers. At high stirring rates, this effect was not occur due to the absence of thick boundary layers; the beta cyclodextrin concentration being too low to significantly increase the drug solubility in the bulk solution.

Tekenaka et al.(1982) showed that amoinophylline has been successfully prepared by spray drying a solution of theophylline and ethylenediamine. DSC data indicated that the strength of the bond between the ethylenediamine and theophylline was affected by the drying temperature. The preparation time was greatly reduced compared to that required using traditional preparative methods which involve several time consuming stages. The packing and flow properties of the complex were found to

be superior to those of the original theophylline particles, which was attributed to their particle shape.

The spray drying for the production of aminopyrine barbital complexes which were dried from feeds incorporating various excipients was investigated by Kawashima et al.(1983). In this study, spray drying complexation and agglomeration were all accomplished in one step. Again, small, spherical particles were produced, but the compressibility was found to be dependent on the particular excipient included in the formulation. When the formulation did not contain any excipient, no product could be recovered from the spray dryer. The drug content of the final product also varied depending on the excipient used, as well as on the drying temperature and the rotational speed of the rotary atomizer. Decreasing the drying temperature or increasing the rotational speed of the atomizer led to an increase in drug content.

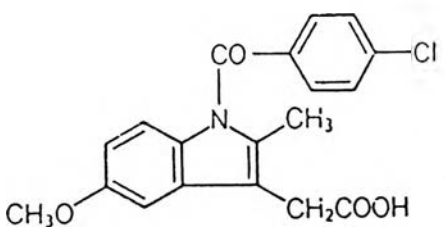
Kawashima et al. (1983) also founded that some oxidation of aminopyrine occurred during spray drying, the degree of which was dependent on the drying temperature, atomizer speed and on the type of excipient used in the formulation. It was observed that the extent of aminopyrine auto-oxidation increased with increasing pH of the feed solution. Increasing the drying temperature increased the degree of auto-oxidation up to a maximum level at 100 °C. At temperatures greater than this, oxidation was reduced, which was attributed to rapid solidification of the droplets in the dryer. The incorporation of additives into the feed solution could significantly reduce the degree of oxidation. The best additives were found to be ethylene diamine tetraacetic acid (EDTA) or glycine. This led the authors to conclude that the additives were reacting with a trace metal in the feed solution which was responsible for catalyzing the aminopyrine oxidation.

Palmieri et al. (1997) evaluated the interactions between methoxybutropate and beta cyclodextrin or hydroxypropyl beta cyclodextrin and the possibility of obtaining inclusion complexes by phase solubility diagram, HPLC, DSC and X-ray diffractometry. Solid inclusion complexes were prepared by spray drying, kneading and solid dispersion. They founded that both cyclodextrins tested can be used to prepare methoxybutropate inclusion complexes even if differences in complexation effectiveness and increasing water solubility are remarkable, depending on the drug-

cyclodextrin molar ratio in the processed powder, on the applied complexation method, and the type of cyclodextrin used. Generally, beta cyclodextrin gives better results than hydroxypropyl beta cyclodextrin in the complexation of this specific drug. Spray drying is by far the best method, particularly if combined with the use of beta cyclodextrin.

Indomethacin

Indomethacin is a non-steroidal, anti-inflammatory agent with anti-pyretic and analgesic properties (Mathew, James and Edward, 1984). Its formula and molecular weight are presented below.



Empirical formula " $C_{19}H_{16}ClNO_4$" (MW = 357.8)

Figure 2 *Molecular structure of indomethacin*

Indomethacin is a white to brownish-yellow, odourless or almost odourless, crystalline powder.The powder was melted, when heated about 158 to162 ^{o}C Dissociation constant (pKa) of indomethacin is 4.5 and the partition coefficient in octanol/aqeous buffer pH 7.4 is 1.0. Solubility of indomethacin was summarized in Table 3.

Indomethacin may exist in at least four polymorphic modifications (Mathew et al.,1984). Melting points of indomethacin polymorphic forms were shown in the Table 4. A solvent-containing 'pseudopolymorphic' modification (mp 90 °C to 100°C) and an amorphous form (mp. 55 °C to 57 °C) were also described. Transition of indomethacin from amorphous form to crystalline form has been found to follow first-order kinetics at 20 °C, 30 °C and 40 °C with half-lives calculated to be 8.12, 3.12 and 0.70 days, respectively.

In aqueous solutions, indomethacin undergoes pH-dependent hydrolysis to 5-methoxy-2-methyl-indol-3-actic acid and p-chlorobenzoic acid (Backensfield et al., 1990). Hydrolysis is generally base-catalyzed although at pH values less than 3, acid catalysis occurs. Base-catalysed hydrolysis of indomethacin has been shown to follow first-order kinetics. Values have been cited for the degradation half-life of indomethacin at room temperature to be about 200 hours in pH 8 buffer, and about 90 minutes in pH 10 buffer (Ban and Usan; 1994). The degradation of indomethacin occurs primary via hydrolysis of the amide moiety. In both acidic and basic solutions the following products are seen.

Indomethacin is unstable to light, both in the solid state and in aqueous solution. Discoloration (darkening) of indomethacin solutions may occur on exposure to light.

Indomethacin has been used effectively in the management of patients with moderate to severe rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, acute painful shoulder (bursitis and/or tendinitis) and acute gouty arthritis. Recently, indomethacin has been found effective in the treatment of neonates with patent ductus arteriosus and in patients with acute cystoid macular edema following cataract surgery.

Table 3 The following solubility data of indomethacin have been reported

Solvent	Temperature (°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]
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	RT	80 mg/100 ml[b]
Ethyl alcohol (95%)	RT	1 in 50
Chloroform	RT	1 in 30
Ether	25	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

From : Klaus Florey, *Analytical Profiles of Drug Substances*, Vol. 13, United States of America, 1994.

Table 4 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
FormIV	134
Type β	158 – 160.5

From : Klaus Florey, *Analytical Profiles of Drug Substances, Vol. 13*, United States of America,1994, p. 211

Cyclodextrins

Structure and Properties of Cyclodextrins

Cyclodextrins are cyclic (α-1,4) – linked oligosaccharides of α - D – glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped. Based on this architecture, the primary hydroxyl groups are located on the wider edge (Figure 3). The most common cyclodextrins are alpha cyclodextrin, beta cyclodextrin and gamma cyclodextrin, which consist of six, seven and eight glucopyranose units, respectively. Chemical and physical properties of the four most common cyclodextrins are given in Table 5. The melting points of alpha, beta and gamma cyclodextrin are between 240 and 265 °C, consistent with their stable crystal lattice structure. (Loftsson and Brewster, 1996).

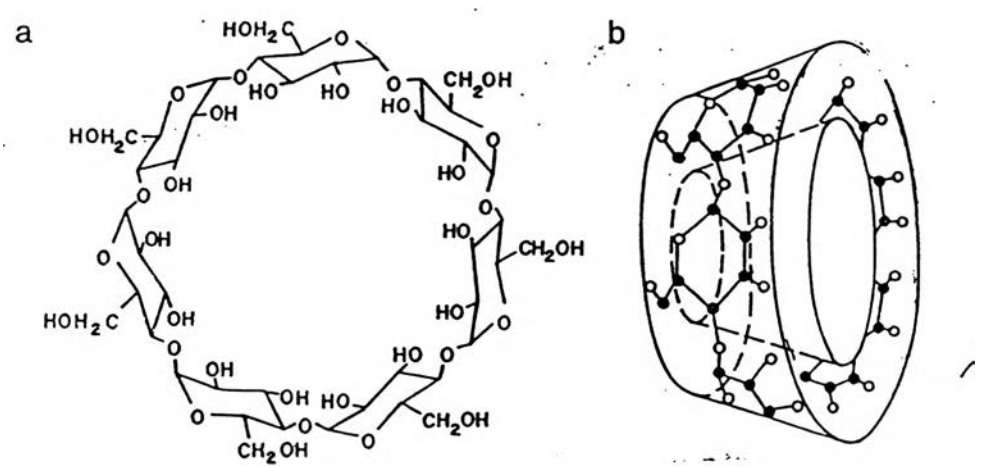


Figure 3 – *(a) The chemical structure and (b) the toroidal shape of the BCD molecule*

The parent cyclodextrins, in particular beta cyclodextrin, have limited aqueous solubility, and their formation with lipophilic drugs, and other compounds with limited aqueous solubility, frequently give rise to B–type phase solubility diagrams as defined by Higuchi (1963). That is, addition of these unmodified cyclodextrins to aqueous drug solutions or drug suspensions often results in the precipitation of solid drug – cyclodexrtin complexes. The aqueous solubility of the parent cyclodextrins much lower than that of comparable acyclic saccharides, and this could partly be due to relatively strong binding of the cyclodextrin molecules in the crystal state (ie. relatively high crystal lacttice energy). In addition, beta and gamma cyclodextrin form intramolecular hydrogen bonds between secondary hydroxyl groups, which detracts from hydrogen bond formation with surrounding water molecules, resulting in less negative heats of hydration (Miyazawa et al., 1995). Thus, intramolecular hydrogen bonding can result in relatively unfavorable enthalpies of solution and low aqueous solubilities. Substituting of any the hydrogen bond forming hydroxyl groups, even by hydrophobic moiety such as methoxy and ethoxy functions, will result in a dramatic increase in water solubility. (Duchene and Wouessidjewe , 1990).

Table 5 Some Characteristics of cyclodextrins

	Alpha	beta	gamma	Sigma
No. of glucopyranose units	6	7	8	9
Molecular weight	972	1135	1297	1459
Central cavity diameter (A°)	4.7-5.3	6.0-6.5	7.5-8.3	10.3-11.2
Water solubility at 25 °C (g/100 ml)	14.5	1.85	23.2	8.19

From : Loftson Thorsteinn and Brewster E. Marcus, *J. Pharm. Sci.*, 85, 1996

In Table 5, it shows the dimension sizes of natural cyclodextims. Each cyclodextrin has a different capability of inclusion complex formation with different sized guest molecules. Alpha cyclodextrin, has the smallest cavity (internal diameter almost 5 A°), which generally too small to include the majority of active ingredients, beta cyclodextrin (internal diameter almost 6 A°) is more convenient. Gamma cyclodextrin (internal diameter almost 8 A°) should obviously be the best one, but it is not in fact intensively produced and remains impossible to use on an industrial scale (Duchene and Wouessidjene, 1990).

The cyclodextrins are crystalline, nonhygroscopic but form various stable hydrates. Cyclodextrins are stable in the solid state if protected from high humidity.

There are various methods to prepare solid dispersion of cyclodextrins. The most common procedure to prepare this solid dispersion is to stir or shake an aqueous solution of cyclodextrin with the guest molecules or its solution. Other methods are freeze drying (Veiga et al., 1996; Erden and Celebi, 1988; Lin , 1991 ; Blanco et al., 1991; Otero, et al., 1992), spray drying (Lin , 1991; Blanco et al., 1991; Otero et al.,1992; Tasic, Jovanovic and Djuric, 1992; Palmieri et al., 1993; Moyano et al.,1999; Boymond and Ridolphi, 1994), kneading (Veiga et al., 1996; Lin , 1991; Blanco et al., 1991; Tasic et al., 1992; Palmeiri et al., 1993), coprecipitation (Nakai et al., 1984; Tokumura et al., 1984; Amdidouche et al., 1989; Sanghavi et al., 1993; Veiga et al., 1996) and neutralization (Tokumura et al., 1984; Erden and Celebi, 1988; Lin et al., 1991). Methods for preparing this solid dispersion without using a solvent are the grinding (Lin et al., 1988) and the sealed heating method (Nakai et al., 1987).

From the review of articles in scientific literature three main groups of methods have been selected: liquid phase, semi-solid phase and solid phase.

1. Liquid phase

1.1 Precipitation of poorly water soluble drug (slow evaporation method)

The drug is slowly added to a saturated aqueous solution of beta cyclodextrin, under intense agitation at ambient temperature for several hours or even days, until spontaneous precipitation of the inclusion complete is achieved. Working in a hot aqueous solution of beta cyclodextrin (60-80 °C depending on thermosensitivity of the drug) increases the beta cyclodextrin concentration in the solution and hence the yield of the preparation. If precipitation does not occur spontaneously after several hours it may be necessary to cool the medium to around 3-5 °C. Alternatively evaporation may be used. This method has the advantages of simplicity. No organic solvent is used but it is a long-winded which offers a low yield of solid dispersion.

1.2 Coprecipitation method

An organic solution of the drug is poured under agitation into an aqueous solution of cyclodextrins. Generally the ratio of drug to beta cyclodextrin is equimolecular, but there is no firm rule. The organic solvent could be isopropanol or dioxane. It might be better to work with a hot solution of cyclodextrin and to maintain heating during agitation. Precipitation is obtained either spontaneously or by evaporation. In contrast to the previous method, it is better to work with a solution of low concentration to avoid any risk of precipitation of pure beta cyclodextrin or pure drug when mixing the two solutions. It is also better to use an organic solvent miscible with water in order to avoid any precipitation of beta cyclodextrin at the water/solvent interface. After the precipitation step, a wash solvent and water, filtration and drying procedure is a pure solid dispersion.

For instance lorazepam (Sanghavi , Choudhari and Viswanathan , 1993) have been encapsulated by this method. The coprecipitation method enables us to obtain a crystalline solid dispersion of high purity. This method has the disadvantages of being too long and needing a large quantity of organic solvent and energy. It is difficult to scale up and there is also a risk of formation of beta cyclodextrin/solvent solid dispersion.

1.3 Neutralization

A method by neutralization has been described. The active ingredient is dissolved as a salt in an alkaline or acid solution containing the cyclodextrin and the solution is then neutralized. This method is applicable for the guests having acidic or basic functional groups. It should be remembered that cyclodextrins are hydrolyzed to be linear oligosacchrides in strong acid solution.

1.4 Spray drying/ freeze drying

These two methods can also be used to dry the solution of beta cyclodextrin and drug. Spray drying and freeze drying are both carried out before any precipitation of the solid dispersion occurs. Freeze drying produces powder that is rough to the touch and with agglomerates which is not the case with spray drying. Inclusion complexes of various drugs, such as and paracetamol (Lin and Kao, 1989), with beta cyclodextrin were prepared by spray drying. The dissolution rate of tablets

formulated from spray dried complex was greater than tablets formulated from physical mixtures. Naproxen (Blanco et al. ,1991 oxazepam (Moyano et al., 1995) could form solid dispersion by spray drying technique and the dissolution rate of solid dispersion was much more rapid than the drugs alone and spray drying gave the best results compared to kneading method.

These methods have the advantages of being faster than the coprecipitation method. There is no waste product to process, the yield of powder formed is higher with freeze drying compared with coprecipitation. The methods are also suitable for soluble substances and it is quit possible to scale them up, particularly the spray drying method. The main disadvantage is that both these methods are expensive, particularly freeze drying. In general an amorphous substance is obtained.

2. Semi-solid phase

2.1 Slurry method

In this case beta-cyclodextrin (one part) is mixed with water (two parts) under high speed stirring to obtain a slurry (about 15 minutes). At this level the drug is added slowly under high speed stirring in 4-72 hours to obtain a thick suspension. The suspension is then dried and ground to give solid dispersion in powder form. This method has low energy consumption, no solvent is used and a high yield of solid dispersion is obtained. The method can also be scaled up. Its advantages are : it takes time and the solid dispersion obtained is less pure than with the coprecipitation method.

2.2 Kneading method

This method is applicable to poorly water - soluble active ingredient consists of first preparing a paste of beta cyclodextrin (10 minutes) by introducing into a kneading machine three parts of beta cyclodextrin and only one part of water. Because of the low solubility of beta cyclodextrin in water 20 °C a paste is formed. The less water there is the better it is, especially when the drug is hydrosensitivity. The second step consists of the progressive addition of the drug to the paste which is mixed for 10 minutes. The viscosity of the mix increases which indicates the formation of the solid dispersion. At this point it is sometimes necessary (for flavoured substances or those

with an unpleasant odour) to add an auxiliary step which involves washing the paste with solvent followed by filtration.

Finally the solid dispersion is dried, either directly in the kneading machine, then grinding to get a fine powder, by oven drying and grinding or by granulation and fluidized air bed drying or freeze drying. This method is very attractive due to its many advantages: the process is short (1-2 hours), simple, inexpensive and solvent free, a low temperature is used (useful for volatile or thermosensitive actives), low levels of water are used which may be useful in avoiding hydrolysis of some actives, excellent yield of solid dispersion and no waste is produced. There is the possibility of production on an industrial-scale.

3. Solid phase

3.1 Grinding method

In this case no water or solvent are used, beta cyclodextrin (1 mole) blended with the drug in a solid state (1 mole) at 20 °C. The mixture formed is then ground, the inclusion complex is obtained by both dynamic and thermodynamic actions. Lin et al. (1988) studied the effect of grinding on the physicochemical properties of ground mixtures of acetaminophen, warfarin, indomethacin, diazepam and hydrocortisone acetate with beta cyclodextrin. They found that acetominophen became amorphous and only formed an inclusion complex. The dissolution rate of drugs from the ground mixtures was shown to be higher than that of the drug alone. This method has numerous advantages: it is simple quick, solvent free, there is no waste, it is easy to scale up. But there are also some disadvantages: it is not applicable to all actives, a partial inclusion obtained, the powder obtained is unstable with risk of obtaining a physical mixture and the inclusion complex may breakdown at high humunity.

3.2 Heating in a sealed container

This academic method is not really applicable on an industrial scale and is only mentioned for the sake of completeness. It has been described for benzoic acid and alpha cyclodextrin. It necessary to mill beta cyclodextrin and the active, then introduce the mixture into a sealed container and heat it to 127 °C

under pressure. The combination ratio is higher than unpressurized samples (Nakai et al., 1987).

If the inclusion complexes are formed in the solid state or solutions, the characterization of these complexes are necessary to be used to identify this formation and needed to use the various methods to explain this formation. Therefore, the detection of these inclusion complexes is divided two categories: detection of inclusion complexation in the solid state and in the solution. These detection techniques are reviewed as the following:

A) Detection of inclusion complexation in solid state

Although there are many techniques to investigate the inclusion complex formation, this section reviews some useful techniques for identification.

1. Powder X-ray diffractometry

When the pattern of a newly formed substance clearly differs from that of an complexed cyclodextrin, complex formation is indicated. Comparison of the diffractograms is only possible if the cyclodextrin as well as guest one, before mixing, treated both identical conditions as the assumed complex because cyclodextrin inclusion complex preparation processes such as freeze drying and grinding, may change the crystallinity of the pure substances and this may also lead to diffraction patterns.

2. Thermo-analytical methods

When guest molecules are included in the cyclodextrin cavity or in the crystal lactice, their melting, boiling and sublimation points are usually shifted to a higher temperature or disappear within the temperature range that the cyclodextrin is decomposed.

3. Infra-red (IR) spectroscopy

IR spectroscopy is used to access the interaction between cyclodextrin and guest molecules in the solid state. The application of IR spectroscopy is limited to guests having some characteristic bands, such as carbonyl or sulfonyl groups.

4. Scanning electron microscopy

This method is used to study the microscopic aspects of the raw materials (cyclodextrin and guest substances, respectively) and the product obtained by cyclodextrin inclusion complex preparation processes.

B) Detection of inclusion complextion in solution

Inclusion complexation of cyclodextrins in solution can be studied by a number of physiochemical method. For example;

Solubility methods: The solubility method or phase solubility analysis was described by Higuchi and Connors (1965). It is used to determine the relationship between the total concentration of drug dissolved and the concentration of added cyclodextrin. This method is based on monitoring changes in solubility of drug by the addition of beta cyclodextrin and changes in solubility of the drug are plotted as a function of beta cyclodextrin concentration. According to the definitions provided by Higuchi and Connors (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 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 investigation 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 cyclodextrin. The solubility constant (Kc) of 1:1 can be calculated from the slope and intercept of the initial straight line portion of the diagram from the following equation:

$$K_{c1:1)} = \frac{\text{Slope}}{S_0(1\text{-slope})}$$

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

Szejtli (1982) evaluated the effect of beta cyclodextrin on the bioavailability of drugs and pointed out the ideal solubility constant should be between 100-1000 M^{-1}. Smaller solubility 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 Figure 4.

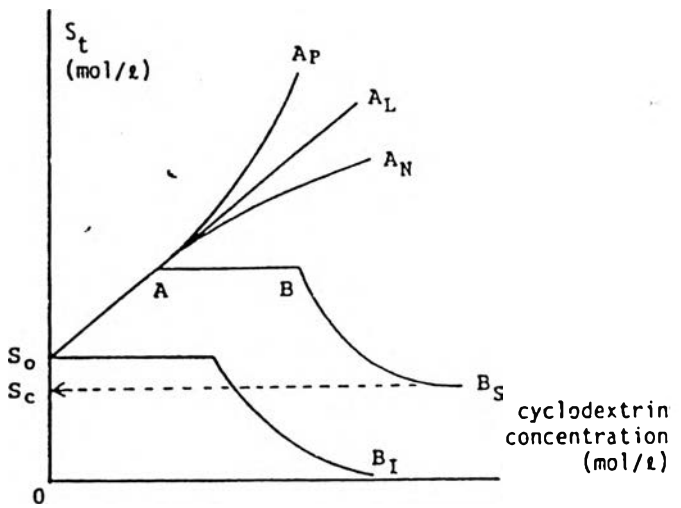


Figure 4 *Phase solubility Diagrams : (A) A-type diagram and (B) B-type diagram*

Application of cyclodextrins for pharmaceutical sciences

Physicochemical properties of guest molecules may be altered if they are surrounded by the hydrophobic environment of cyclodextrin cavity. They may lead to suitable formations for potential drugs. The most obvious possible alteration is an enhancement of the solubility and in pharmacy, this is generally intended to improve bioavailability.

1. Enhancement of the solubility and the rate of dissolution of poorly water-soluble drugs

The cyclodextrin solid dispersion of a poorly water-soluble drug is usually more hydrophobic than the free drug itself. The occurance of an increased solubility can be concluded from a phase solubility diagram. Physical mixtures of slightly water soluble or insoluble drugs and cyclodextrins often have faster dissolution rates than drugs alone. If a crystalline drug is dispersed over a hydrophilic matrix, as in the case with mechanical mix system with cyclodextrins, the particular drug will be passively carried into the dissolution medium as the carrier dissolves and this may increase the dissolution rate.

Furthermore, the increase in dissolution rate of inclusion complexes may also be due to the decrease in crystallinity of this solid dispersion. A compound in the crystalline state dissolves more slowly than that in the amorphous state. Processes to prepare inclusion complexes, such as grinding and freeze drying lead to a decrease in crystallinity or even to amorphous powders.

Casella et al. (1998) studied the solubility and dissolution behavior of indomethacin containing with beta-cyclodextrin. Five trimolecular complexes of indomethacin, ammonia and water prepared with beta cyclodextrin (prepared by recrystallization). The results show indomethacin was improved by complex formation with beta cyclodextrin. There was little difference among the various complex solubilities. Indomethacin dissolution profiles were found to differ and were unrelated to either the complexed indomethacin content or binding constant. Indomethacin dissolution profiles were found to be related to the complex crystallinity and enthalpy.

Different solid dispersion of indomethacin and both beta-cyclodextrin and hydroxypropyl beta cyclodextrin were prepared using different methods: kneading, spray drying and neutralization followed by freeze drying. It was shown that the type of product obtained can depend on the preparation procedure: the neutralization method leads to the inclusion of sodium indomethacin, whereas indomethacin in the acid form appears to be induced in the cyclodextrins by the spray drying method. The kneading method did not lead to a real inclusion. The indomethacin dissolution rate from the solid dispersion is clearly increased compared with that of the physical mixture and indomethacin alone (Lin et al., 1991).

In general, it can be concluded that the increased dissolution rate of cyclodextrin-entrapped drug molecules is a result of various factors: an increased solubility, an improved wettability, molecular dispersion and the large surface area available for dissolution.

2. Enhancement of the bioavailability

The bioavailability of an orally administered drug depends on several factors, among them the dissolution rate, solubility and the rate of intestinal absorption. Following the rate administration of a drug alone, the drug may dissolve slowly and incompletely in the gastro-intestinal tract. Since orally administered drugs must dissolve in the aqueous medium of the gastrointestinal tract prior to absorption, the improvement of the solubility and the rate of dissolution of poorly soluble drug can be seen as first steps towards an improvement in oral bioavailability.

In case of a drug-cyclodextrin complex both dissolution and dissociation determines the amount of free dissolved drug. The degree of dissociation is determined by the complex stability constant or solubility constant, K_c. Dissolving the complex, it partly dissociate until equilibrium. The inclusion complex with a small complex constant dissociates readily. The free active ingredient, which is generally hydrophobic, is presented in the molecular state to the liquid mucosa of the gastrointestinal tract, and easily reabsorbed, resulting in a displacement of the previous equilibrium, and with the appearance of the new free molecules of active ingredients.

Hamada et al. (1975) studied the interactions of alpha cyclodextrin and beta 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 increase with the addition of beta-cyclodextrin while not with glucose. Szabo et al. (1989) reported a significantly increase in dissolution of chloramphenicol was found by the physical mixture of chloramphenicol and beta cyclodextrin. The improvement of dissolution of the physical mixtures was attributed to the combined effects of the hydrophilic properties of beta cyclodextrin and fragmentation of chloramphenicol crystal. Simple physical mixture of drug with beta 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 complexes of progesterone and beta cyclodextrin. They found that dissolution of all formulations containing beta cyclodextrin were much faster than those with microcrystalline cellulose.

Lin, et al. (1987) reported the enhancement of pharmaceutical activity of Cerm 3276 when grinding with beta cyclodextrin although no inclusion was formed. In tablet manufacturing, cyclodextrin can be used as an auxillary substance (disintegrant, binder or diluent). Shangraw et al. (1990) reported the compatibility of tablet using cyclodextrin as a filler has excellent but the fluidity was insufficient for routine compression.

3. Rectal and dermal administration

Reducing the hydrophobicity of drugs by cyclodextrin may also improve percutaneous on rectal absorption. A number of reports concerning the enhanced blood or serum levels of drug after rectal administration of suppositories containing a drug-cyclodextrin complex have appeared.

4. Parenteral administration

Despite of cyclodextrins are extremely useful in many applications, parenteral applications of drugs complex by natural cyclodextrins are very limited. The solubility of cyclodextrin is not satisfactory for injectables and it appears to be toxic when given parenterally, precluding its use in intravenous and other parenteral formulations.

Hydroxypropyl beta cyclodextrin is relatively harmless when administered parenterally and may serve as solubilizer.

5. Enhancement of physical and chemical stability

Many drugs can be stabilized against degradation processes such as hydrolysis, oxidation, volatilization, sublimation, decomposition by heats, reactions with other components. Backenfeld et al. (1990) examined the effects of a number cyclodextrinbs and cyclodextrins derivatives on the stability of indomethacin aqueous solution. Beta cyclodextrin was obserbed to have the most favorable ring size for the stabilization of indomethacin at pH 7.4. Further, the p-chlorobenzoic part of the indomethacin molecule was included in the cyclodextrin channel. The derivatives studied (in particular, those of either gamma or beta cyclodextrin) also reduced the extent of hydrolysis, especially the derivatives that had lipophilic (for example, methyl or ethyl) substuents. The solubilising effect was greater as more hydroxy groups of glucose moiety were substituted.

6. Reduction of side effect and toxicity of drugs

Complexation may decrease toxic side effects of drug administration. It has been demonstrated that the ulcerogenic character of indomethacin (Lin et al., 1991) could be reduced by beta cyclodextrin complexation (prepared by neutralization followed by freeze drying).

Cyclodextrin complexation may also be used in detoxification processes and decreased a bitter or irritant taste.

From the above application of cyclodextrins in pharmaceutical sciences there are many uses of cyclodextrins for further studying especially the improvement of solubility and stability properties of cyclodextrin some studies showed the inclusion compounds of indomethacin and cyclodextrin. For example, Kurozumi et al. (1975) investigated that the inclusion compounds of non-steroidal antiinflammatory drugs with alpha cyclodextrin and beta cyclodextrin were prepared by the freeze drying and the coprecipitation method. The freeze-drying method was successful in obtaining the inclusion compounds of all the test drugs with beta cyclodextrin and also some of them with alpha cyclodextrin by obtaining their aqueous solutions with addition of aqueous

ammonia before the process, with a very good yield compared with the usual coprecipitation method. It was shown by X-ray diffractometry that the inclusion compounds obtained by the freeze drying method were amorphous. This study found that the p-chlorobenzoic part of indomethacin molecule was included in the cyclodextrin cavity (Figure 4).

The inclusion complex of indomethacin sodium salt in beta cyclodextrin has been studied by proton NMR at high magnetic field (Djedaini et al., 1990). This technique was used to evidence the formation of a soluble 1:1 aqueous solution at physiological pH and association constant of inclusion complexes including the possible model of indomethacin if experimental procedures are carefully designed.

Sodium Lauryl Sulfate (Ainley and Weller, 1994)

Sodium lauryl sulfate is an anionic surfactant used in a wide range of nonparenteral pharmaceutical formulations and cosmetics. It shows as a detergent and wetting agent effective in both alkaline and acidic conditions.

1. Description

Sodium lauryl sulfate consists of white or cream to pale yellow - coloured crystals, flakes or powder having a smooth feel, a soapy, better taste and a faint odor of fatty substances.

Empirical Formula : $C_{12}H_{25}NaO_4S$

Molecular weight : 288.38

2. Typical properties

Sodium lauryl sulfate is freely soluble in water, giving an opalescent solution and practically insoluble in chloroform and ether. pH of 1% w/v aqueous solution is 7.0-9.5. The melting point has been reported as 204-207 °C (for pure substance). At 20 °C, critical micelle concentration is 8.2 mmol/L (0.23 g/L).

3. Stability and storage conditions

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e. pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate.

The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.

4. Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants causing loss of activity even in concentration too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions.

Solutions of sodium lauryl sulfate (pH 9.5-10.0) are mildly corrosive to mild steel, copper, brass, bronze and aluminium. It also incompatible with some alkaloidal salts and precipitates with lead and potassium salts.

5. Applications in pharmaceutical formulation or technology

Surfactants have been widely in pharmacy to facilitate the formulation of poorly soluble drugs in solution dosage forms. They have also been used to increase the stability of drug substances (Suleiman and Najib , 1990).

Otsuka and Matsuda (1995) showed that phenytoin combined with various kinds of surfactants at 40 %w/w such as sodium lauryl sulfate, sodium deoxylate and the sucrose ester of stearic acid by a cogrinding method, compared with drug without surfactant, dissolved very rapidly and gave constant drug concentrations after 10 min.

The effect of nonionic and ionic surfactants on the alkaline hydrolysis of indomethacin was investigated (Sulieman and Najb , 1990). The nonionic surfactant polysorbate 80, produced a 7-fold increase in the stability of indomethacin. The ionic surfactants (cetromonium bromide, benzalkonium chloride and sodium lauryl sulfate) also resulted in an increase in the stability of indomethacin but to lesser than polysorbate 80.

Cipiciani et al. (1985) showed that anionic micelles of sodium lauryl sulfate which inhibit hydrolysis of indomethacin in an alkaline solution.

The other use of sodium lauryl sulfate in the pharmaceutical preparations are described in Table 6.

Table 6 Applications of using sodium lauryl sulfate in pharmaceutical

Use	Concentration (%)
Anionic emulsifier, forms self-emulsifying bases with fatty alcohols	0.5-2.5
Detergent in medicated shampoos	≈ 10
Skin cleanser in topical applications	1
Solubilizer in concentrations greater than critical micelle concentration	> 0.0025
Tablet lubricant	1-2
Wetting agent in dentrifices	1-2

From : Wade Ainley and Weller Paul J., *Handbook of Pharmaceutical Excipients*, Washington DC, 1994.