CHAPTER II

LITERATURE REVIEW

1. Principle of Solid Dispersion.

The term solid dispersion was first used by Mayersohn and Gibaldi (1966). "Solid-state dispersion" and was employed to increase dissolution rate of water- insoluble drug.

However the clear definition was introduced by Chiou and Riegelman (1971a). Solid dispersion is a system which one or more ingredients were dispersed in an inert carrier or matrix in the solid state prepared by melting (fusion), solvent (coevaporation) or melting-solvent method

The dissolution rate of active ingredients in solid mixture containing more than one component is influenced by the other components. The Choice of carrier plays the important role to the dissolution rate of active ingredient in solid dispersion system. Some carriers release an active ingredient faster than the others. From this point of view, solid dispersion can be applied for both sustained release and fast release.

1.1 Preparation method of solid dispersion.

1.1.1 Melting method (Fusion method)

Sekiguchi and Obi (1961) were the first group that employed this method . Sulfathiazole and Urea were first physically mixed. Then the mixture was heated until thoroughly fused. Rapid cooling in ice bath was applied to entrap sulfathiazole particles in the urea matrix.

This procedure was used extensively thereafter. The cooling rate was found important in such a way that the size of crystal and physical state of active ingredient depend upon. Usually the faster cooling, the better dissolution rate.

Several cooling methods were studied e.g. iron plate containing circulated cold air/water (Chiou and Riegelman, 1969; 1971b), and cooled aluminium plate (Pederson and Rassino, 1990)

Mcginity et al. (1984) studied on tolbutamide–urea solid dispersion and found that tolbutamide has formed more amorphous state in the process with fast cooling than that of slow cooling. In general, drug in amorphous state has better dissolution than drug in crystalline state.

There are three main advantages of this method. Firstly, melt method is simple and economy. Secondly this method does not require solvent where sometimes may cause toxicity. Lastly , when this method is used in conjuction with quenching (rapid cooling) technique, drug molecules can be supersaturated

in the matrix hence finer drug crystallization. These crystals are much finer than those of simple eutectic mixture.

However there are some disadvantages found in this method. Choice of carriers is limited. Carriers with low melting point are preferred.

Decomposition of drugs or carriers can be encountered especially at high temperature during melting. Some carriers decomposes at the temperature close to their melting points, for instance, succinic acid. Melting in a close container or in the vacuum atmosphere is therefore required for those types of carriers.

1.1.2 Solvent method (Coevaporation method)

Solvent method is the technique where the solvent is used to dissolve both drug and carrier. The mixed solution is then evaporated to remove the solvent. Evaporation can be either under atmospheric or vacuum condition. The solid obtained after evaporation is the coevaporate of drug and carrier where drug is suspended in the carrier network.

A number of researches have been conducted with this method such as griseofulvin-PVP (Mayersohn and Gibaldi, 1966), griseofulvin-PEG6000 (Chiou and Riegelman, 1969), miconazole-PEG4000 (Pederson and Rassino, 1990) and probenecid-phospholipid (Habib, Azadi and Akooteran, 1992)

Advantages of this method is the ability of using carriers with high melting point (this is where melting mothod is limited) and less decomposition of drug and carrier. This is because high temperature exposure can be avoided. Generally, most solvents are easily evaporated.

However, there are a number of disadvantages concerning to this method.

a. The preparation cost of solvent method is higher than that of melt method. The main costs are from incorporation and removal of solvent.
b. Too much effort is needed to completely remove liquid solvent.
c. Preparing time is quite long. It is therefore affecting the chemical stability of key ingredient.
d. Cosolvent is difficult to be determined as, in most cases, carriers are hydrophilic whereas drugs are hydrophobic.
e. Theoretically, reproducing similar crystal form by this method is hardly possible.

1.1.3 Melting-solvent method.

This method is meant to overcome the disadvantages of both melting and solvent methods. It is prepared by , firstly, dissolving the drug in a solvent. Then incorporating the solution directly into liquid water-soluble carrier. Then the solvent is evaporated to gain the solid . However, some issues may occur in this method, for example, the selected solvent or dissolved drug may not be miscible with melted water-soluble carrier. Polymorphic form of the drug in solid dispersed form can be affected by selection of solvent used in the first stage.

The key advantage of this method is its compatibility to heat labile drug. However the advantage is unsuitably to high dosage drug (not more than 50 mg) also, polymorphic form of drug suspended in a carrier sometimes can be affected by liquid solvent used.

Pharmaceutical applications were found on employing this method. Some examples are spironolactone-PEG6000 (Chiou and Riegelman, 1971a) and miconazole nitrate-sodium hydroxide using ethanol as a solvent (Pederson and Rassino, 1990).

1.2 Mechanism of solid dispersion formation.

The basic, but main, principle of increasing solubility by using solid dispersion method is the altering physicochemical structures. The physicochemical structures of dispersions play an important role in controlling their drug release from matrix. There are six representative structures outlining interaction between carrier and drug. (Ford, 1986)

a. Simple eutectic mixtures.

b. Solid solution.

c. Glass solution and glass suspension.

d. Amorphous precipitation in a crystalline carrier.

e. Compound or complex formation.

f. Combination.

a. Simple eutectic mixtures

Simple eutectic mixtures can be prepared by melting two components followed by rapid solidification. The two components must show complete miscibility in the liquid state and negligible solid-solid solubility. Eutectic systems are characterized as a crystalline component. It can be explained by a phase diagram. Both components are crystallized out simultaneously in very small particle sizes. The increment of specific area is the main contributor to increase a dissolution rate.

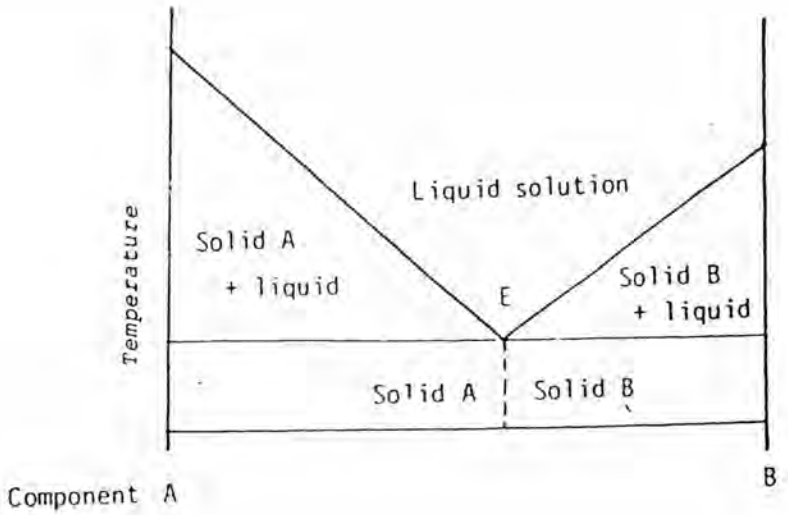


Figure 1 Phase diagram of an eutectic with negligible solid solubility
E: Eutectic point

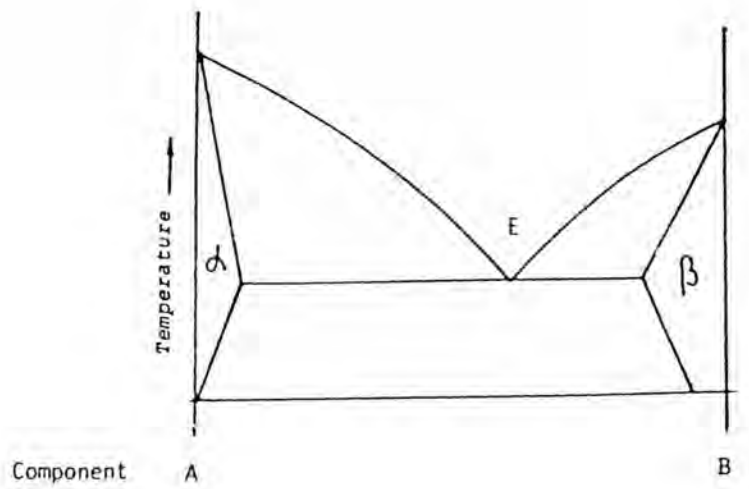


Figure 2 Typical phase diagram of a discontinuous solid solution of binary system A and B . α and β are regions of solid solution formation E: Eutectic point

b. Solid solution.

Solid solution is derived from solid solute dissolving in solid solvent. Both of which are crystallized together, usually called mixed crystals, in a continuous one-phase system. Goldberg, Gibaldi and Kanig (1965) suggested that a low water soluble drug which solid dispersed in high water soluble carrier will show higher water solubility than that in eutectic mixture. This phenomenon can be explained by the particle sizes. In the eutectic mixture system, drug particles will be much coarser than that of solid solution system. This is due to the molecular dispersion of drug in the system. In addition, the advantage of being formed a solid solution is the lesser solvent needed to dissolve the same amount of solute.

Goldberg, Gibaldi and Kanig (1966) demonstrated that solid solution of griseofulvin-succinic acid had dissolution eight times greater than that of eutectic mixture system.

Two types of structures are used to represent solid solution. On the basis of their solid miscibility, they may be classified as "continuous or discontinuous solid solutions"

The main criteria for differentiation of these two structures is the bond strength between the same component versus the bond strength between the different molecules. For continuous solid solutions, it possesses to the bond strength between the different components greater than the bond strength between the same molecules, and therefore the components are miscible throughout the composition range. This seems to be unrealistic and so far no solid dispersions are classified into this category.

Discontinuous solid solution is an opposite. Each component is capable of dissolving the other to some extent.

c. Glass solution and glass suspension.

Glass solution is a single homogeneous phase containing solute dissolving in a glass solvent. Glass state is created by melting glass solvent with solute and cooling down rapidly. It is often characterized by transparancy and brittleness below the glass transforming temperature.

Since the intermolecular bonding between solute and solvent may be increased in solid solutions. For glass solution, the bond is not as strong as lattice bonding of solid solutions (Chiou and Riegelman, 1969). The bond within the glass solution is just similar to that in the liquid solution. The dissolution rate of the drug in glass solution is therefore theoretically faster than that in the solid solution. Several compounds have been proven to initiate glass solution e.g. sucrose, glucose, ethanol and 3-methylhexane.

Molecules with polyhydroxy group also have potency of glass solution formation. This phenomenon can be explained in terms of the strength of hydrogen bond. These types of molecules have strong hydrogen bonds that help prevent crystallization. Instead they transform into glass solution.

Glass solution is preferred to solid solution when preparing a fast release solid dispersion because of its higher rate of dissolution. The bond between solvent and solute in solid solution is often greater than that in glass solution. Additionally glass solution is more viscous than solid solution. This causes inhibition effect to drug crystallization. As a result, supersaturation level is likely to be achieved.

At certain drug to carrier ratios, other carriers may favour glass solution including PVP, urea and PEG. Glass suspensions rather than glass solution are formed when the drug and carrier do not show interaction and are immiscible in the liquid state.

d. Amorphous precipitation in a crystalline carrier.

Instead of forming an eutectic mixture where both drug and carrier crystallize from a melting or solvent method, drug also can behave differently by precipitate out in an amorphous form in the crystalline carrier.

Mixture containing long chain polymers may crystallize slowly and because of steric hindrance will never reach 100% crystallinity. Consequently dispersion in PEGs and other long chain polymers may show gradual increases in crystallinity of amorphous areas during storage.

Sekiguchi and Obi (1961) reported that amorphous of sulfathiazole in crystalline urea was the first key factor that enhanced drug absorption in human via oral administration

Chiou and Riegelman (1971a) found precipitated amorphous of iopanoic acid under electron microscope when PVP10000 was used as carrier.

Mcginity, Maincent and Steinfink (1984) investigated tolbutamide-PEG system by employing X-ray diffraction method. It was found that amorphous of tolbutamide presented in the freshly prepared system.

e. Compound and complex formation.

This system is very difficult to generalize the influences. This is where some compounds and/or complex are formed. Complex formation is characterized by an enclosure of the drug molecule in the carrier molecule. The hollow space inside a molecule or a group of molecules of the carrier is therefore required. Many soluble carriers readily form soluble complexes with drugs hence improve the drug solubility.

Cyclodextrins, microbiologically modified from starch, are one of the current carriers with this property. "Cyclo" means circle and dextrin means starch. The ring of these dextrins have different internal diameters depending on the number of glucose units present in the molecule.

f. Combination.

In any system of solid dispersion, the combined mechanism can occur. This is from where the concept arised. Dispersion may be a combination of drug-carrier interactions. Usually phase interactions are often difficult to qualify because the structures of the dispersions being often dependent on the methods of preparation and age of dispersion.

1.3 Mechanism of increased dissolution rates.

The increased dissolution rates from solid dispersions are attributed to the reduction of particle size of the drug within the dispersions, molecular dispersions and wettability.

Particle size reduction is the primary factor in improvement of dissolution yet not the most powerful factor considered particle size reduction of drug as a predominant factor in controlling the release from chloramphenicol-urea solid dispersion. However particle size reduction has offered to a certain level of increase dissolution rates, which is a minimum level, molecular state is mostly preferred and expected.

Molecular dispersions is where the carrier dissolves intimately with the drug. Molecular dispersions are obtained in glass and solid solution and possibly in amorphous dispersions as described previously. In some cases, dependent mainly upon the carriers used, complex can be formed. These are where solid dispersion technique has an advantage over traditionally physical size reduction.

Chiou and Reigelman (1971b), Ford (1986), Bloch and Speiser (1987) and Acarturkl, Kislal and Celebi (1992) have reported the mechanisms that enhance solubility in a very similar manner. Following mechanisms are summarized from those reports.

a. Particle size reduction in eutectics.
b. Deaggregation and deagglomeration.
c. Changing crystallinity of drug into a metastable form.
d. Changes in microenvironment of drug.
e. Water soluble complex formation.
f. Increase wettability.
g. Combined effects.

a) Particle size reduction.

As described earlier, for the eutectic mixtures, the major contribution to enhance drug solubility is the size reduction of crystals. Table below shows the size of particles liberated from different carriers and compositions. (Ford, 1986)

Table 1 The size of particles liberated from solid dispersions.

Dispersion	Method of preparation	Type of particles liberated	Size (microns)
10% testosterone in PEG6000	Melt	Crystals	1-50
10% testosterone in PEG1000	Melt	Crystals	1-5
10% testosterone in PEG6000	Solvent	Crystals	1-10
10% testosterone in PVP11,500	Solvent	Amorphous	0.5-10.
3% primidone in citric acid	Melt	Crystals	5.2± 0.3
21% primidone in citric acid	Melt	Crystals	4.7± 0.3
5% indomethacin in PEG6000	Melt	Amorphous	0.5-3.0
10% tolbutamide in P 40S	Melt or Solvent	Crystals	3-10

b) Deaggregation and deagglomeration.

In general, aggregation and agglomeration reduce the specific surface area thereby reducing accessibility of solvent to the drug. Aggregation describes a group of molecules bind together with strong intermolecular bonds or same type of molecules binding with strong bonds. Whereas agglomeration describes a lump of molecule loosely bind together with weak bond e.g. the

bond between different charges. In theory, aggregated molecules are more difficult to breakdown than that of agglomeration.

Solid dispersion has improved this concern. The drug will be surrounded by inert carrier which acts as a barrier to prevent aggregation and agglomeration.

c) Changing crystallinity of drug into a unstable form or amorphous.

Interest of drug cystalline transformation are mainly studied in two main areas which are polymorph and amorphous.

Polymorph

Polymorph is the term describes solid crystalline phase where at least to two different arrangements are possible (Haleblian and McCrone, 1969). Polymorphism is therefore characterized as any element or compound that have more than one distinct crystal species. Different polymorphs generally are different in structure and properties due to the crystals of two different molecular arrangment. These properties, for instance, are solubility, melting point, density, hardness, crystal shape, optical and electrical properties and vapour pressure.

For solid dispersion system, there are a number of publications illustrating this mechanism. sulfathiazole-urea, sulfathiazole-povidone and Indomethacin-PEG are some of the illustrations.

Chiou and Niazi (1971) have reported the change of polymorphism of sulfathiazole dispersing into urea has improved the dissolution rate of sulfathiazole alone. Simonelli, Mehta and Higuchi (1976) identified the form of sulfathiazole that controls its dissolution rate in the solid dispersion with urea. They have considered several forms of sulfathiazole such as polymorps form (Sulfathiazole form I, form II), glassy state and coevaporate form.

Solid dispersion of indomethacin and PEG4000 was investigated by Ford (1985). It was found that polymorphism of indomethacin has changed from form I to form II resulting in higher dissolution rate.

Amorphous

Amorphous is the highest energy form of the pure drug. As the third rule of thermodynamics explains that a system with lower energy is more stable than that of higher energy. Amorphous is not an exception. Amorphous will produce faster dissolution than the crystalline whether the crystals are dispersed in a carrier or not.

Simonelli, Mehta and Higuchi (1976) showed in their work of the sulfathiazole and povidone where they concluded that an amorphous state of sulfathiazole is the controlling phase for both solubility and dissolution rate.

The form of nifedipine by rolling mixing with PVP was studied by Nozawa, Mizumoto and Higashide (1986). It was found that nifedipine crystals in the roll mixture with PVP at the content PVP 25% seemed to be converted easily to the amorphous state. The X-ray diffraction pattern shows a distinctive peak for the roll mixture with 25 % PVP.

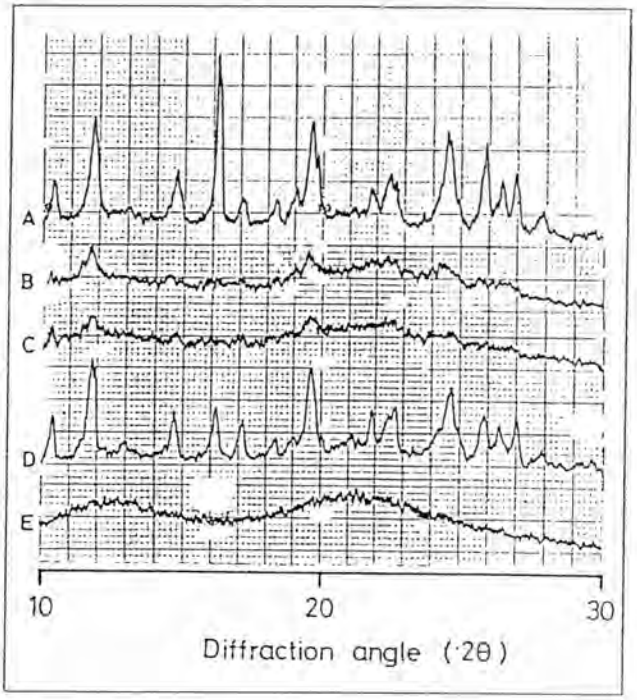


Figure 3 X-ray diffraction pattern of various mixed systems with PVP K-30
(A) PVP content 50%, physical mixture (B) 25%, roll mixture
(C) 50%,roll mixture (D) 25%, coprecipitate (E) 50%, coprecipitate

d) Changes in microenvironment of drug.

An increase in dissolution can be made by changing the microenvirnment of the drug. For instance, when environments surrounding the drug have been improved to be more soluble, the higher drug solubility can be anticipated. The factors that help improve microenvironments include surface tension reduction, viscosity, destruction of hydrogen bond etc.

The surface tensions were evaluated between nifedipine alone, nifedipine with water-soluble gelatin, β-cyclodextrin and egg albumin. It was found that reduction of surface tension is one of the factors contributing to increase dissolution rate. (Acarturk, Kislal and Celebi 1992)

Table 2 Surface tension of samples measured by the ring method

Compound	Surface tension (dyne/cm)		
	Alone	Kneaded mixture	Physical mixture
Nifedipine	65	-	-
Water-soluble gelatin	49	49	60
β-cyclodextrin	69	59	67
Egg albumin	58	56	56

Urea is an another carrier which has been proved to destruct the hydrogen bond of water hence increasing enthalpy. As a result, the higher drug level dissolved in the solvent was obtained (Feldman and Gibaldi,1967). Corrigan and Timoney (1975) have also used the similar principle to explain the influence of PVP on the dissolution properties of hydroflumethiazide.

Viscosity has shown the effect on the drug in two ways; positively and negatively. Firstly, it reduces degree of crystallization consequently inducing supersaturated drug in the matrix. This can be simply explained as the matrix can hold higher amount of drug hence it is called supersaturation. This gives the positive effect to the dissolution rate. Suzuki and Sunada (1998) studied on the influence of water soluble polymer on the dissolution of nifedipine solid dispersion with combined carriers. It was evidenced that the crystallization behavior of nifedipine was inhibited by a supersaturated solution containing hydroxypropyl methylcellulose and PVP. They reported that the use of a

polymer with high compatibility and adhesion with nifedipine provides a higher supersaturation level of the drug.

Secondly, viscosity however can reduce the dissolution rate, especially when surfactant is used. Morita and Hirota (1982) studied the effect of polysorbate80, which is a surfactant, on the dissolution rate of benzoic acid. It was reported that the dissolution rate of benzoic acid was initially increased when the percent of polysorbate80 increased. However when the percent of polysorbate80 increased further, the dissolution rate of benzoic was decreased as a result of viscosity increment.

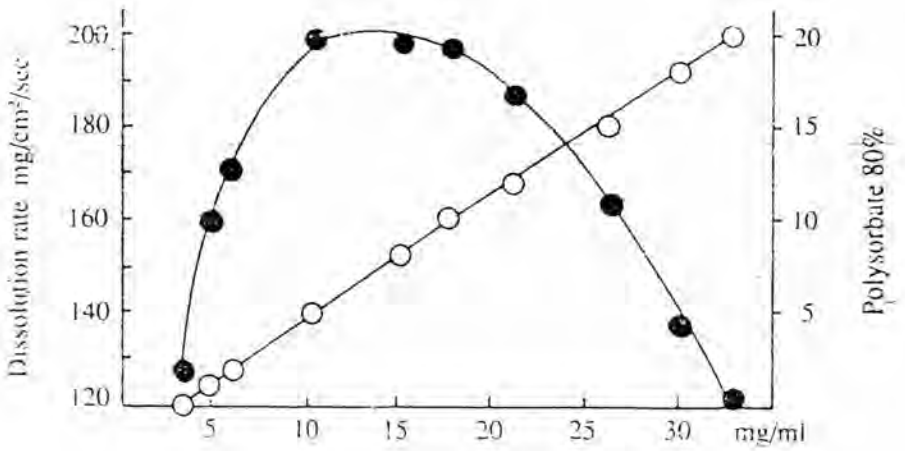


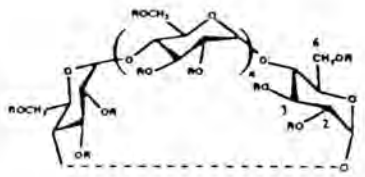
Figure 4 Relationship between dissolution rate of benzoic acid at 25 °C and percent of polysorbate80. -●- dissolution rate, -o- concentration.

e) Water soluble complex formation.

As mentioned earlier that water soluble complex can be formed . β-cyclodextrin has been studied extensively as it shows a great potential to improve poorly water soluble drug. Corrigan and Stanley (1982) comprehensively studied the mechanism of drug dissolution rate enhancement from drug- β-cyclodextrin system. β -cyclodextrin itself is hydrophilic and has a hollow structure where can be filled by hydrophobic drug. It therefore improves hydrophilicity of the drug.

Sometimes the method based on this knowledge is called complex inclusion. There are a number of reports on the applications of these properties. (Duchen, Vaution, and Glomot, 1986; Nakai et al., 1990a; Nakai et al., 1990b; Nakai et al., 1991; Acarturk, Kislal and Celedi, 1992; Watanabe et al., 1996; Becirevi-Lacan et al., 1996; Hirayama, Wang and Uekema, 1994; Kedzierewicz, Hoffman, and Maincent, 1990 and Ahmed et al., 1993)

Table 3 General structure of commonly used cyclodextrins and their abbreviated names.



Cyclodextrin	Abbreviation	*R*	*n*
α-cyclodextrin	α-CD	H	4
β-cyclodextrin	β-CD	H	5
γ-cyclodextrin	γ-CD	H	6
Carboxymethyl-β-cyclodextrin	CM-β-CD	CH_2CO_2H or H	5
Carboxymethyl-ethyl-β-cyclodextrin	CME-β-CD	CH_2CO_2H, CH_2CH_3 or H	5
Diethyl-β-cyclodextrin	DE-β-CD	CH_2CH_3 or H	5
Dimethyl-β-cyclodextrin	DM-β-CD	CH_3 or H	5
Methyl-β-cyclodextrin	M-β-CD	CH_3 or H	5
Random methyl-β-cyclodextrin	RM-β-CD	CH_3 or H	5
Glucosyl-β-cyclodextrin	G_1-β-CD	glucosyl or H	5
Maltosyl-β-cyclodextrin	G_2-β-CD	maltosyl or H	5
Hydroxyethyl-β-cyclodextrin	HE-β-CD	CH_2CH_2OH or H	5
Hydroxypropyl β-cyclodextrin	HP-β-CD	$CH_2CHOHCH_3$ or H	5
Sulfobutylether-β-cyclodextrin	SBE-β-CD	$(CH_2)_4SO_3Na$ or H	5

[a] Derivatives may have differing degrees of substitution on the 2, 3 and 6 positions

f) Increased wettability.

Solid dispersion has shown the advantage on wettability over pure drug. Theoretically, water will diffuse toward the drug so as to wet the drug surface and then diffuse to the centre. A poorly water soluble drug prepared by solid dispersion shows an increase in wettability. A carrier with excellent water soluble acts as a bridge. The drug is surrounded by the carrier which can be easily dissolved in water. This causes solvent to contact with drug faster.

Mohamnad and Felle (1983) studied the wetting and dissolution rate of phenobarbitone powder and reported that wettability is the first process to occur followed by drug dispersion into liquid phase and solubility. A poor dispersion drug can be improved by incorporation of a surface active agent.

g) Combined effects.

Combined effects, a self descriptive, are characterized as the combination of the mechanisms mentioned above. Combined effects are usually found in many cases.

2. Carriers

2.1 Selection of suitable carriers.

Selection of best carriers is one of the most critical factors to successful increased dissolution rate. A carrier chosen should meet the following criteria (Ford, 1986)

a. The carrier should not be harmful or remaining any toxic residues in the system.

b. It should be water soluble with intrinsic rapid dissolution property.

c. The carrier must fulfil the requirement of specified methods e.g.

Fusion method:

The carrier should be chemically, physically and thermally stable with a low melting point. Excessive heat during dispersion process can be easily encounter in fusion method. Low melting point is usually preferred. Chemical interaction between drug and carrier should be also avoided. Ideally the carrier should solidify rapidly and completely into a stable discernable solid. This will

help maintain the drug as a fine crystalline dispersion. Or else the carrier may solidify through a viscous state which help maintain the drug in a near molecular dispersion. Miscibility between drug and carrier is important otherwise subsequent irregular crystallization may occur on cooling which may give variable dissolution.

Solvent method:

The carrier should dissolve in a variety of organic solvents. It should be able to pass a vitreous state. This is where the carrier should inhibit or retard drug crystallization. As a result, drug concentration is maintained at or near the molecular dispersion state. Cocrystallization between drug and carrier is compulsory otherwise a solid dispersion will not be achieved.

d. As a rule of thumb, a carrier should increase the aqueous solubility of the drug. However there are some studies showed that it is not compulsory e.g. sulfathiazole-urea (Sekiguchi and Obi, 1961 and Chiou and Niazi, 1971) which urea was shown to reduce the aqueous solubility of sulfathiazole.

e. The carrier, in the solid state with the drug, should not form strongly bonded complexes with a strong association constant which may reduce dissolution rates.

f. The carrier should not show any pharmacological effect which may interfere the resultant solid dispersion.

2.2 Application of selected carriers in solid dispersion system.

2.2.1 Polyethylene glycols (PEGs)

Polyethylene glycols (PEGs) is one of the predominant polymers in this field and has been extensively studied. The molecular weight fraction of PEGs employed for solid dispersion vary from 1000 (soft uncutious solids) to 20000 (hard brittle crystals) (Craig, 1990)

a) Properties of PEGs

The polymers in this molecular weight range are semi-crystalline, containing both ordered and amorphous components. In the crystalline state, the chains have the structure of double helices. Each repeating unit contains approximately 15 monomers.

The helices are arranged as plate-like structures (lamellae) from which the hydroxyl end groups are rejected onto the surface. Therefore PEG is highly water soluble. The chain within the lamellae may be extended or folded, the latter being metastable with respect to the former. The melting characteristics of PEGs have been studied extensively due to the stability of the metastable folded chain forms compared to those of other polymers. Studies using DSC show the folded chain has additional endothermic peaks at temperature below that corresponding to the stable extended chain.

The molecular size of the polymers favor the formation of interstitial solid solution with drugs and their viscous properties at temperature just above their freezing points retard crystallization and favor supercooling of the drug. A

shorter cooling time may lead to the higher production of small crystals compared to a longer cooling time. The high viscosity of solid PEG may also lead to a sluggish precipitation of metastable crystals.

b) Solid dispersion of drug-PEG.

The early work done by Chiou and Riegelman (1969) showed that the dissolution rate of griseofulvin were increased by dispersion into PEG4000, PEG6000, PEG20000 using melting and solvent methods. The urinary excretion in dogs for 6- demethylgriseofulvin revealed 88% absorption from 10% melted griseofulvin-PEG6000 compared with 100% from pure PEG4000 solution, 45% from commercial capsule and 33% from commercial tablet. X-ray diffraction and aqueous solubility studies suggested that the marked enhancement of dissolution and absorption rate of griseofulvin-PEG solid dispersion was primarily due to the reduction of the size of griseofulvin crystals rather than to the formation of solid solution, complexation or metastable polymorphic forms.

On the other hand, Ravis and Chen (1981) suspected that for the system of dicumarol-PEG4000 prepared by melting method, partial polymorphic conversion and solid solution were the attractive explanation to substantial dissolution rate increment.

Allen and Kwan (1969) attempted to determine the ratio of crystalline drug dispersed at the molecular level (a)in a drug-polymer system which behaves as a supercooled liquid solution and (b) in a drug-carrier system which apparently forms true solid solutions. Indomethacin-PEG6000 acted as a supercooled liquid solution whereas sulfathiazole-urea represented a solid solution. In two diverse system, it was shown that under appropriately chosen

conditions, the dissolution rate of the drug was linearly related to its degree of crystallinity at molecular level.

Most other studies emphasized on illustration of increased dissolution rate of sparingly water soluble drugs. Ford (1986) reviewed a number of applications of PEG in solid dispersion, for instance;

-Steriods i.e. prednisolone acetate, 17-methylestosterone, hydrocortisone acetate, betamethasone alcohol and testosterone.

-Sulphonamides.

-Hypoglycemics i.e. chlorpropamide, tolbutamide, acetohexamide.

-Diuretics i.e. hydroflumethiazide, hydrochlorothiazide, bendrofluazide and furosemide.

-Bepridil.

-Phenylbutazone.

-Diazepam.

Current studies include p-aminobenzoates-PEG6000 whose mechanisms of dissolution was reported. Sjokvist-Saers and Craig (1992) found that the aqueous solubility decreased logarithmically with molecular weight of the carrier (PEG6000), whereas a linear increase was found between solubility and initial rate.

Ahmed et al. (1993) studied comparative dissolution between bropirinine-β-cyclodextrin inclusion complex and its solid dispersion with PEG6000 by solvent method. It revealed that the solid complex of bropirinine with β-cyclodextrin exhibited a markedly faster dissolution rate compared to the solid dispersion with PEG6000 for bropirinine.

PEG6000 and β-cyclodextrin have been also applied with hydrochlorothiazide (Simonelli et al.,1994). It was found that both carriers formed amorphous state and increased in dissolution rate over the pure drug. Similar study was done by Veiga and Espanol (1995). Instead of hydrochlorothiazide, oxodipine was used. Guyot et al., 1995 have also applied those two polymers aimed at improving dissolution of norfloxacin. The achievement was reported.

c) Influence of PEG molecular weight.

As there are many grades of PEG available, several studies have attempted to draw a conclusion on the effect of molecular weight on the dissolution rate.

In general, the dissolution rates of the pure polymers decreased as the molecular weight increased. When several molecular weights of PEG were applied in different drug-carrier systems, the exact conclusion cannot be drawn. This means that in some cases the lower molecular weight of specific polymers, the worse dissolution rate is obtained and also some cases it may show an opposite result.

The systems where the dissolution rates decrease with decreasing molecular weight of PEG include papaverine, sulphamethoxydiazine and hydrochlorothiazide such phenomenon may be explained as ;

-The higher molecular weight PEGs may form higher viscous solutions thereby further reducing drug crystallization.

-The higher molecular weight PEGs may increasingly favor the incorporation of drug as solid solutions.

-The higher molecular weight PEGs may merely flake more readily during dissolution.

The other system is where the dissolution rate of drug dispersed in PEG decreased as the molecular weight increased. This system includes indomethacin, hydroflumethiazide, sulphadimadine and tolbutamide. The explanations to such system are probably made on the basis of the dissolution rates of the PEG weight fraction themselves and the incorporation of a drug into the low molecular weight PEG may produce a eutectic temperature below 37 °C hence allowing melting of the dispersion to occur prior to actual dissolution and further enhance dissolution rate (Ford, 1986)

2.2.2 β-cyclodextrins

a) Properties of β-cyclodextrin.

Cyclodextrins are cyclic oligosaccharide composed of 6-8 glucose units joined through α 1,4 linkage. α-cyclodextrin contains 6 glucose units while β and γ –cyclodextrins contain 7 and 8 glucose units respectively. Table 3 is the summary of important characteristics of α, β and γ-cyclodextrins.

In term of cyclodextrin structure, the C-1 chair conformation of the glucose monomers imparts to the molecule, like a cone-shaped structure. The narrow end of the torus contains primary hydroxyl groups on C-6 whereas another end, the wider end, contains the secondary hydroxyl groups on the C-2 and C-3 of the glucose units being located on the torus.

Table 4 Some important characteristics of cyclodextrins.

	α	β	γ
Molecular weight	972	1135	1297
$[\alpha]_D^{25}$	+150.5 ± 0.5	+162.0 ± 0.5	+177.4 ± 0.5
$[\alpha]_{344}^{25}$	+1160	+1165	
$[\alpha]_{194}^{25}$	+ 741	+ 798	
Diameter of cavity	4.7–5 Å	8 Å	10 Å
Volume of cavity	176 Å³	346 Å³	510 Å³
Number of water molecules taken up by cavity	6	11	17
Diffusion constant of 40 °C (Craig, Pulley, 1961)	3.443	3.224	3.000
Crystal form (from 60% aq. isopropanol)	Hexagonal plates or blade shaped needles	Monoclinic parallelo-grams	Quadratic plates or prisms
Solubility in water g/100 ml, 25 °C	14.5	1.85	23.2
Molecules per unit cell	4	2	6
Water of crystallization, %	10.2	13.2–14.5	8.13–17.7

As the interior of the molecule are relatively lipophilic and the exterior relatively hydrophilic, it shows a tendency to form inclusion complex. This is one of the most interesting of cyclodextrins. A molecule which may form inclusion complex only have to satisfy a single condition which is adaptable entirely, or at least partly to the cavity of the cyclodextrins. Most adaptable drugs form1:1 complexes with cyclodextrin.

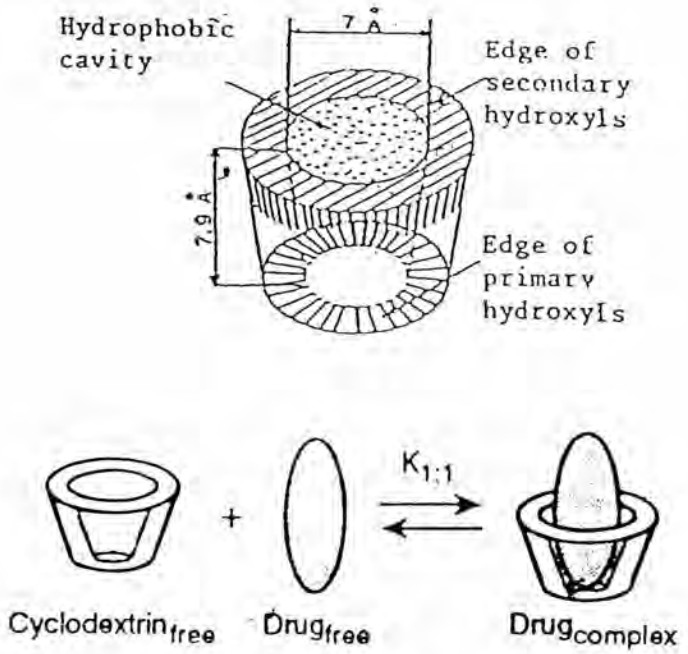


Figure5 Functional structural scheme of cyclodextrin and its association to form a drug; drug-cyclodextrin complex (Stella and Rajewski, 1997)

Inclusion compounds are usually prepared in a liquid medium. In the case of water-soluble materials, a guest drug is added to an aqueous solution of cyclodextrin. The mixture is then heated with continuous agitation for several hours or days depending on type of systems. The inclusion complex precipitates spontaneously or by cooling. The mixture can also be freeze-dried or spray-dried.

For a sparingly water soluble drug, it will be dissolved in the appropriate organic solvent. Drug solution is then added to a hot aqueous cyclodextrin solution with agitation. Crystallization takes place within the following hours or days.

b) Solid dispersion of drug-β-cyclodextrin.

β-cyclodextrin has been reported to form inclusion complexes with variety of drugs. In early days, main focus of inclusion complexes was on the complex formation in solution. Until recently the field of study has expanded to those formation in solid state and this is where solid dispersion is involved. Kurozumi, Nambu and Nakai (1975) cited by Corrigan and Stanley (1982) reported the possibility of complex formation by a freeze drying process.

Corrigan and Stanley (1982) have comprehensively explored the mechanism of increased drug dissolution rate from β-cyclodextrin-drug system and freeze dried system. The two classical theories, namely a soluble complex model and a carrier controlled model were reviewed. Physical mixed system and freeze dried system were in comparison.

Their conclusion is that if crystalline drug is dispersed in the carrier, as is the case of physical mixed system, particulate drug will be passively carried into the dissolution medium as the carrier dissolves. This system gives an intermediate dissolution rate.

For the freeze dried system, in this case was bendrofluazide-β-cyclodextrin, the inclusion complex was found. The dissolution rate would follow the soluble complex model. Furthermore, if the freeze drying produce smaller drug crystallites, the drug dissolution rate should be higher than those of the corresponding mechanical mixture.

Mayano et al.(1997) investigated a similar comparison in gliclazide-β-cyclodextrin system with various preparation methods. For spray dried, the

dissolution enhancement was mainly contributed from the formation of an inclusion complex in the solid state and from the reduction of the crystallinity of the products. Whereas the main contributing factor for physical and kneaded mixtures was only due to the wetting effect of the β-cyclodextrin.

Nakai et al. (1990a) studied the interaction of clobazam with cyclodextrin in both solution and solid state. For ground mixture of clobazam with natural cyclodextrin (unmodified), hydrogen bond between the two carbonyl groups of clobazam and hydroxyl groups of natural b-cyclodextrin was detected and yet no inclusion complex was formed. On the other hand, clobazam with heptakis-(2,6-di-o-methyl)-β-cyclodextrin was further employed in inclusion compound formation of benzoic acid (Nakai et al.,1990b and Nakai et al.,1991) and p-nitrophenol (Watanabe et al.,1996)

Other interesting modified β-cyclodextrins is the group of hydroxypropyl-β-cyclodextrins. Becirevic-Lancan et al. (1996) studied the complex formation between nifedipine and β-cyclodextrin and β -cyclodextrin derivatives; hydroxypropyl- β-cyclodextrin and heptakis (2,6-di-o-methyl)- β-cyclodextrin in freeze dried, spray dried and physical mixed systems. Heptakis (2,6-di-o-methyl)- β-cyclodextrin was found to be the best solubilizing agent and freeze dried solid dispersion showed the highest dissolution rate due to high inclusion complex formation. However, similarly to the findings of Mayano et al., 1997, physical mixture was not evident of inclusion complex formation.

Other applications of hydroxypropyl-β-cyclodextrin group to other drugs were also studied. Methoxybutropate (Palmieri et al., 1997) and Lonidamine (Palmieri, Wehrle and Martelli., 1998) are some of the examples.

2.2.3 Poloxamers.

a) Properties of poloxamers.

Poloxamers can be classified as nonionic surfactant and they consist of a-b-a copolymers of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene). The properties of polyethylene and polyoxypropylene can be altered. This alteration results in change of the total molecular weight and the relative hydrophilicity of the surfactant. The nomenclature given to poloxamer has its own interpretation. The first two numbers multiplied by 100 approximate to the molecular weight of the hydrophobe, whilst the third number multiplied by 10 gives an estimate of the content of polyoxyethylene in percentage.

b) Solid dispersion of drug-poloxamers.

In the past few years, a greater attention has been drawn to poloxamer derivatives as another carriers for solid dispersion applications. This is due to a well documented articles have been printed on dissolution improvement of slightly water drugs when poloxamer derivatives were employed.

Reddy, Khalil and Gouda (1976) reported a marked increase in the dissolution rate of digitoxin and digoxin by solid dispersing the drugs into poloxamer188 and deoxycholic acid. The mechanism was thought to be crystalline modifications.

Luhtala (1992) investigated the effect of poloxamer184, a nonionic surfactant, on crystal growth and aqueous solubility of carbamazepine. Poloxamer 184 was found to retard water-mediated phase transformation and

the consequent crystal growth. It also changed the crystal habit, more importantly, the solubility properties of carbamazine has been changed.

The more comprehensive study was done on the mechanism of action of poloxamer in changing crystal properties (Mackellar et al.,1994).

The experiment was done on ethyl p-hydroxybenzoate as a model drug. Poloxamer resulted in decrease particle size and a change to a prismatic habit. The decrease in particle size of drug crystals was shown to be correlated with the molecular weight of the polyoxyethylene chain in the poloxamer, if the molecular weight of the polypropylene is kept constant. These effect only occurred after a threshold concentration had been stimulated. It was shown that poloxamer do affect solution viscosity and relative supersaturation operating during crystallization. These factors however do not cause any affect on crystal appearance. Instead, it was proposed that poloxamers adsorbed onto the surface of hydrophillic faces of the crystal to exert this effect on the crystal properties causing a subsequent inhibition of crystal growth.

3. Nifedipine and Its Properties.

3.1 Pharmaceutical properties

Chemical structure.

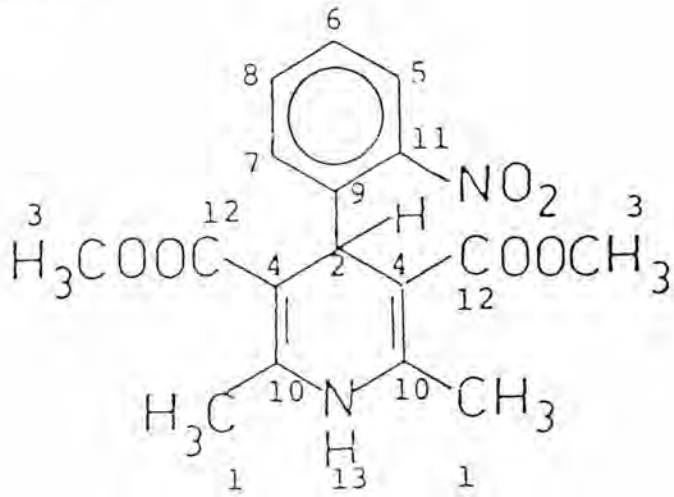


Figure 6 Nifedipine structure.

Empirical formula	: $C_{17}H_{18}N_2O_6$
Molecular weight	: 346.34
Chemical name	: Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine dicarboxylate.
	: 3,5-Pyridinedicarboxylic acid,1,4-dihydro-2,6 dimethyl-4-(2-nitrophenyl)-, dimethyl ether (The United States Pharmacopoeial Inc, 1990)
Description	: A yellow crystalline powder. Melting point 171 °C to 175 °C

Solubility : Easily soluble in acetone, chloroform, less soluble in ethanol, practically insoluble in water. Very light senstive in solution (Windholz et al., 1983)

Nifedipine, an oral calcium-blocking agent is widely used clinically as a coronary vasodilator and for the treatment of hypertension, angina pectoris and other cardiovascular disorders.(Sorkin, Clissold and Brogden,1985) It shows very slightly water solubility (11μg/ml at 37°C in distilled water) and exhibits poor dissolution characteristics (Kohri et al.,1987).

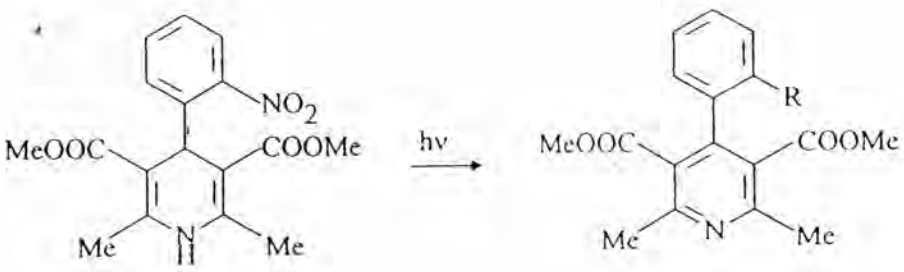
Nifedipine physiological action is inhibition of transmembrane influx of extracellular calcium ions across the membranes of myocardial cells and vascular smooth muscle cells, without changing serum calcium concentration (McEvoy, ed., 1989)

The usual dose is 10 mg three times daily. It may also be administered by injection via coronary angiography and balloon angioplasty (Reynolds, ed.,1989)

Oral dose of nifedipine is rapidly absorbed from the GI tract approximately 90%. Only 65-75% of the oral dose reaches systemic circulation as unchanged drug since nifedipine is metabolized on first pass through the liver. Peak serum concentration are reached within 0.5-2 hours after oral administration. The therapeutic range in plasma is 25-100 μg/l.

3.2 Photostability

As nifedipine or 4-(Nitrophenyl)-1,4-dihydropyridines has an aromatic nitro group which is often photoactive, degraded rapidly in sunlight. The nitro group is reduced to nitroso while the ring is oxidized. The product after exposure to sunlight is shown in Figure 7a but under UV irridiation the nitroso group is reoxidized to give b. ($R = NO_2$)



Nifedipine a. R=NO b. $R=NO_2$

Figure 7 Exposured to sunlight and UV products of nifedipine.

Nifedipine is one of the highly unstable drugs. In daylight, nifedipine solution shows high photosensitivity depending on light intensity. Nitrosophenylpyridine and nitrophenylpyridine derivatives are photodegradation products from exposure of nifedipine solution to daylight. Only one minute during the month of May, $t_{90\%}$ is attained compared with $t_{90\%}$ in November (Thoma and Klimek, 1985a and b cited by Tonnesen, 1996).

Azoxy derivative is one of the two other decomposition products which has been detected in small amount after irradiation in the solid state (Figure 8).

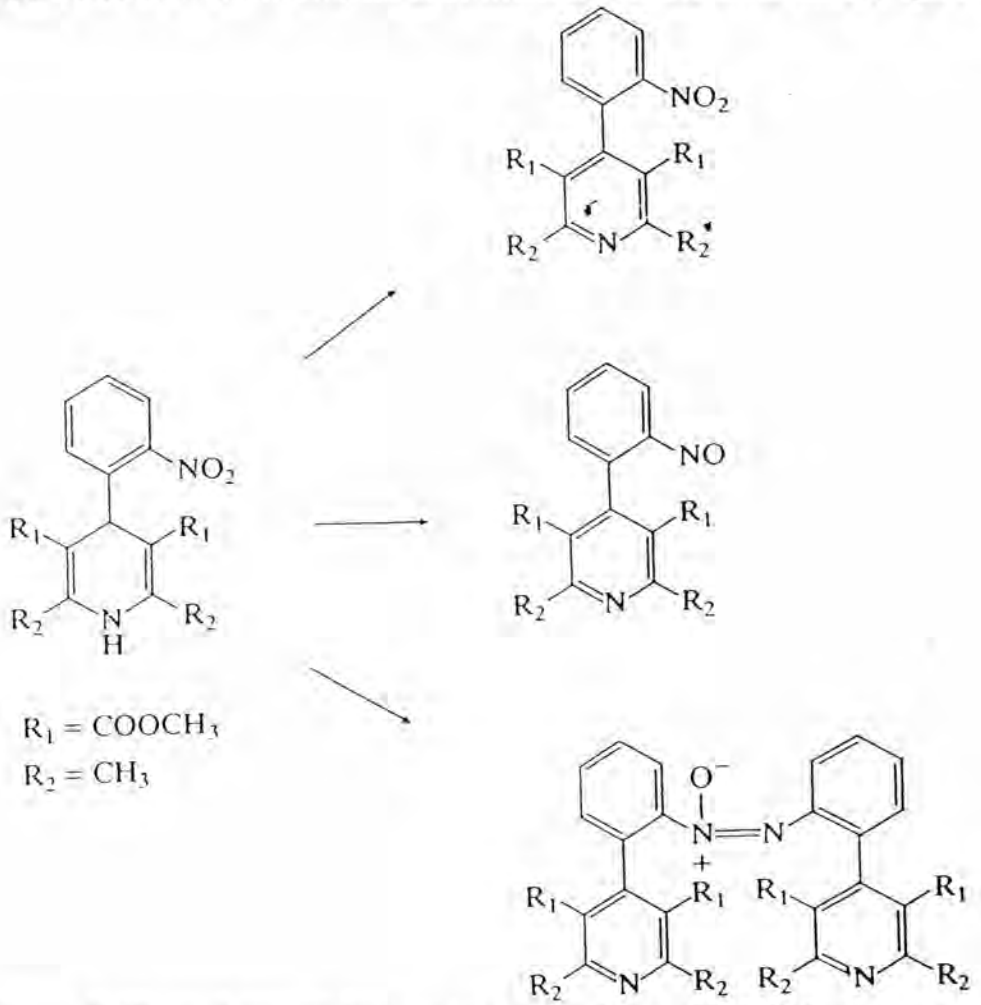


Figure 8 Photochemical decomposition products of nifedipine:
(1) nitrophenylpyridine derivative; (2) nitrosophenylpyridine derivative;
(2) azoxy derivative.

There was a report on which photodegradation of nifedipine in the crystalline state and in solution were compared. Within 40 minutes, 20% of the crystalline nifedipine decomposed. During the next 80 minutes no further degradation, but nifedipine solution decomposed completely during this period (Figure 9), (Thoma and Klimek, 1985 cited by Tonnesen 1996).

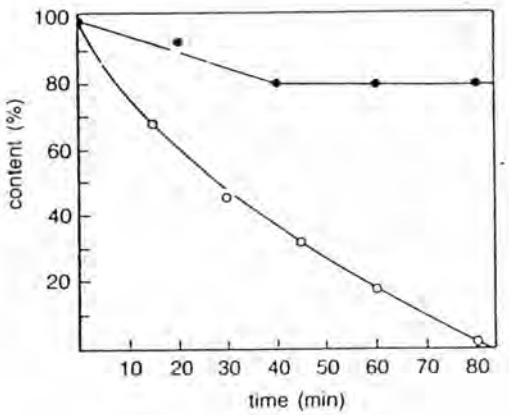


Figure 9 Photoinstability of nifedipine crystals (≤ 5μm) compared with nifedipine solution :- •- nifedipine crystals; -o- nifedipine solution, C_o = 3mg/50ml

In terms of the influence of the wavelength to absorption spectrum of nifedipine, Figure 10 shows that the solution is stable down to a wavelength of 475 nm. Photolysis starts exactly at the point where nifedipine absorption begins at 450 nm. Photolysis increase considerably up to about 400 nm. Nifedipine is thus completely degraded by light in the rather long-wavelength region within 10 minutes.

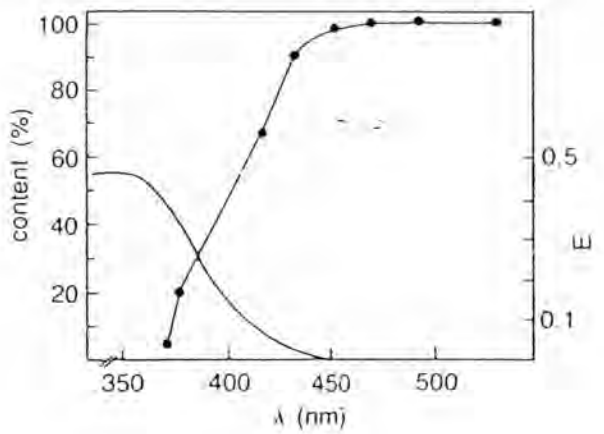


Figure 10 Influnce of the wavelength of the irradation light on the photostability of nifedipine :- •- dependence of the residual concentration on the wavelength of xenon radiation (left ordinate) ; — long-wavelength section of the nifedipine adsorption spectrum (right ordinate)

3.3 Approaches to determine nifedipine concentration.

The determination of nifedipine and its oxidized degradation products has been subjected to many investigations. A high performance liquid chromatography procedure for identification and separation of nifedipine and its metabolites in oral nifedipine formulation has been employed for the analysis of the photo-oxidation products of the the drug (Grundy, Kherani and Foster, 1994).

Also, there is a report of using selective gas chromatographic method with electron capture detection analogous to determine nifedipine concentration in plasma (Abrahamsson et al., 1998). The determination of nifedipine concentration was conducted based on one lamda spectrophotometric method (Benita, Barkai and Pathak, 1990 and Yamamura and Rogers, 1996)

However a direct and simple spectrophotometric method for simultaneous determination of both nifedipine and its oxidized degradation products were proposed despite their overlapping UV absorption spectra (Al-Turk et al., 1989). The analysis of both nifedipine and its oxidized degradation products in this investigation is based on the measurement of absorbance values at two wavelengths. The subsequent calculation of the concentrations of the two components in the mixture is required by solving for two simultaneous equations.

4. Applications of Solid Dispersion Used in Nifedipine System.

Several attempts were made to improve dissolution rate of nifedipine by applying solid dispersion techniques. Sugimoto et al. (1980) are one of those early candidate worked in this area. Nifedipine was coprecipitated in polyvinylpyrolidone. It was claimed that amorphous form was found at the drug to the carrier of 1 to 3. An X-ray diffraction patterns containing 1:3 and 1:9 weight ratio of nifedipine to PVP was found to be difference and was suspected an occurance of amorphous, This was confirmed by DTA result when endothernic peak accompanied with the melting point of nifedipine (171°C) was disappeared in the coprecipitate containing 1:3 ratio of nifedipine to PVP. However DTA result was not actually shown in the publication, only X-ray diffraction resulted were found. The mechanism proposed was not clearly visualised.

The effect of particle size of solid dispersion was also reported. The 12-16 mesh size, 48-60 mesh size and less than 145 mesh size.were found to have little effect on the dissolution rate of the drug. The study in beagle dog was shown that the C_{max} and AUC were 5-fold and 3-fold increase respectively for the drug to the carrier ratio of 1:3.

Nifedipine –PVP system was further studied. Nozawa, Mizumoto and Higushide (1986) implemented roll mixing principle to increase dissolution rate of nifedipine. Nifedipine exhibited favorable dissolution rate than those in the system of coprecipitate and physical mixture. Types of PVP used were selected by preparing nifedipine roll mixed with various PVPs: PVP K-15, PVP-K30 and PVP-K90 respectively. PVP K-30 was the most favorable additive for nifedipine system among the three when taking dissolution rate into the consideration. The appropriate roll mixing time was chosen at 60 min. Many diffractive peaks derived from nifedipine crystal almost disappeared overlapped by that of PVP during the roll mixing even for 15 min. Authors suspected that there was an indication of entire crystal changed to an amorphous state. However they have pointed out that disintegration of drug crystal may be attributed to defects of crystal lattice resulted from compression force between rollers. Nevertheless, it was clear that drug crystal in roll mixed system with 25% of PVP K-30 was far more disappeared than that of the coprecipitate system.

Yamamura and Rogers (1996) comprehensively studied the effect of lattice distortion if nifedipine crystals and an amorphous state of phosphatidylcholine on dissolution behaviour of nifedipine in its binary systems with phosphatidylcholines. The physicochemical properties of nifedipine, dipalmitoyl phosphatidylcholine and dimyristoyl phosphatidylcholine in

physical mixtures, coprecipitate and ground mixture were investigate in relation with dissolution behaviour of nifedipine in such system.

Dipalmitoyl phosphatidylcholine was found existed in an amorphous form in the ground mixture whereas in the physical mixture and coprecipitates dipalmitoyl phosphatidylcholine presented in a crystalline state. This was confirmed by disappearances of both correspondent peak in X-ray diffraction and the correspondent endothermic peak in DSC spectra.

From the studies of lattice parameters; C-axis and full-width at half-maximum, of X-ray diffraction suggested that the lattice distortion of nifedipine crystals in the ground mixture was larger than that in the coprecipitate.

It was concluded that the improvement of dissolution rate of nifedipine from nifedipine-phosphatidylcholine ground mixtures is strongly dependent upon the physicochemical state of both nifedipine and phosphatidylcholine. A distortion of nifedipine crystal lattice and an amorphous state of phosphatidylcholine are some of the contributions to those improvement.

It should be noted here that phosphatidylcholine itself is not a carrier. It was described as forming colloidal aggregates (liposomes) in the dissolution medium in which drug partitioned and dissolved during dissolution.

Law et al. (1992) have previously incorporated phosphatidylcholine in nifedipine-PEG solid dispersion. It was reported that incorporation of phosphatidylcholine have resulted in a 2.6 and 2.2-fold increase in nifedipine initial dissolution rate and dissolution after 60 minutes respectively. There were two main mechanisms explained. One of which was an amorphous formation of nifedipine. Another factor attributed to the phosphatidylcholine in the solid

dispersion system was the formation of lipid vesicles entrapping some dissociated nifedipine molecules. Also the lipid-soluble nifedipine molecules could be accommodated in the bilayer structure of the phosphatidylcholine vesicles, the dissolution rate therefore was enhanced. The latter mechanism was investigated under microscope.

PEGs have also been employed as the other carriers to nifedipine solid dispersion. Save and Venkitachalam (1992) prepared nifedipine-PEG solid dispersion by melt method aimed to improve nifedipine solubility in aqueous. Two types of PEGs; PEG4000 and PEG6000 were used to compare with physical mixture. Both physical mixed and solid dispersion systems showed and increase in dissolution rate of nifedipine. For physical mixture, the explanation was based on the solubility effect by the carrier operating in the microenvironment of the drug. For a system of solid dispersion PEG, whose gave higher solid dispersion, the mechanisms were primarily contributed to the transformation from crystalline state to the other less stable forms.

The best performing ratio between drug to carrier was found at 1:10.It was suspected that at this ratio the drug might exist in a metastable form at the saturation point, the point at which the system exhibits maximum enhancement in solubility. Above this saturation point, as the percentage of carrier increased, the longer time required for diffusion of the drug from the matrix probably resulted in a slightly decreased dissolution rate.

Suzuki and Sunada (1997) have compared nicotinamide, ethylurea and PEG6000 as carrier for nifedipine solid dispersion prepared by melt and physical mixed materials. From the solubility study of nifedipine in presence of those carriers; nicotinamide show about 2 times stronger solubilizing effect than those of PEG6000 and ethylurea. Since ethylurea and PEG have amino or

hydroxyl groups and hydrophobic groups, it was suspected that both groups interfere with the water structure and the formation of hydrophobic interaction which finally affected the solubilization of the drug.

The dissolution profiles of the solid dispersions clearly showed that the dissolution rate of nifedipine from solid dispersions with ethylurea or PEG was much higher than that from the physical mixtures. However the difference in dissolution rate between the physical mixtures and the solid dispersion with nicotinamide was not substantial.

In the X-ray diffraction pattern, the identity peak of 7.9, 10.3 and 11.7 at 2θ for crystalline nifedipine in both physical mixed and solid dispersed with nicotinamide were found. The intensity of these peaks were similar when compared with the same ratio but different preparation methods, suggesting that the entire amount of the drug exist as a pure crystalline phase in the solid dispersion. The phenomenon was explained by solubilizing effect. It was predicted that the higher the solubilizing effect of a carrier, the smaller the difference in the dissolution rates between physical mixture and solid dispersion.

Solubility enhancement with combined carriers was also studied by incorporating hydroxypropylmethylcellulose into the nifedipine-ethylurea, -PEG6000 and –nicotinamide. Nifedipine solid dispersion with a single carrier improved the drug dissolution rate, but there was not a remarkable increase in the drug solubility. This may be due to the presence of drug crystallinity. Hydroxypropylmethylcellulose was found effective in forming an amorphous nifedipine in solid dispersion with nicotinamide and ethylurea.

The combined carriers were again employed in their later work (Suzuki and Sunada, 1998). It was concluded that the use of a polymer with high compatibility and adhesion with nifedipine provides a high supersaturation level of the drug during dissolution. For the selection of combined carrier, solubility and miscibility if any combined carrier to the primary carrier and the drug are the useful factors to consider.

It should be addressed that the similarity between the findings concerning nifedipine-PEG6000 system by Save and Venkitachalam (1992) and Suzuki and Sunada (1997). The transformation of crystalline nifedipine to amorphous form was nit found in the work done by Suzuki and Sunada (1997) at the drug-carrier ratio of 1:5. Similarly, Save and Venkitachalam (1992) suggested that the saturation point for metastable from nifedipine was at the drug-carrier ratio of 1:10.

Very few publications reported the solid dispersion of nifedipine with poloxamers. One of which was the study done by Khidr (1994). The result was just briefly mentioned that poloxamer407 had showed a positive outcome in improving dissolution rate of nifedipine.

β-cyclodextrin and its family have also shown an improvement of nifedipine dissolution rate. Acarturk, Kislal and Celebi (1992) studied that interaction of nifedipine with water soluble gelatin, egg albumin and β-cyclodextrin in solid state prepared by kneading method. β-cyclodextrin and water soluble gelatin were found significantly increase in the dissolution rate of nifedipine as compared to pure drug. The enhanced dissolution rate of nifedipine from nifedipine-β-cyclodextrin system may be caused by the

solubility effect. It was reported that the inclusion complex of nifedipine and β-cyclodextrin had not been completely formed in the solid state.

Hirayama, Wang and Uekama (1994) have studied the effect of 2-hydroxypropyl-β-cyclodextrin on crystallization and polymorphic transition of nifedipine in solid state. The key finding was the glassy nifedipine in 2-hydroxypropyl-β-cyclodextrin matrix was converted to the metastable form of nifedipine, form B, in the non isothermal heating. When it was stored below the crystallization and transition temperatures, metastable form B was converted to the stable form A. As a result, 2-hydroxypropyl-β-cyclodextrin is useful for selection of preparation method of from B as a fast dissolving form of nifedipine.

5. Method for Determination Characteristic of Solid Dispersion.

5.1 X-ray powder diffraction.

The diffraction method is the most powerful tool in solid state studies especially for studying the physical nature of solid dispersion. A diffractogram serves as the drug's fingerprint which markedly different from those of the compound or complex formation. In this method, the intensity of the X-ray diffraction from a sample is measured as a function of diffraction angles. Various studies of solid dispersion has been used this method (Portero, Remunan-Lopez and Vila-Jato, 1998; Guyot et al.,1995)

5.2 Differential scanning calorimetry (DSC).

DSC has proved a powerful tool in evaluating the drug-carrier interaction. The physical or chemical changes are automatically recorded as a function of temperature or time as the substance is heated at a uniform rate. Ageing characteristics and stability problems may also be predicted from this method.(Ford and Timmins,1989)

5.3 Infrared (IR) spectrophotometry.

Infrared spectrophotometry is the method of determination between the interaction of drug and carrier in solid dispersion system. If the IR band do not deviate from the drug, it suggests that there is no interaction between drug and carrier. If the band is broaden and different from the pure drug, it indicates that there might be some interactions such as complex formation, hydrogen bond.

5.4 Scanning electron microsopy (SEM).

This is the method where sample was scanned under microscopy. It can actually see what appearances of particles. This method is often used to characterize morphology, particle size, shape, surface and appearance.