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Solid Dispersions as a Drug Delivery System

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ABSTRACT − Solid dispersion, defined as the dispersion of one or more active ingredient in a carrier or matrix at solid state, is an efficient strategy for improving dissolution of poorly water-soluble drugs for enhancement of their bioavailability. Compared to other conventional formulations such as tablets or capsules, solid dispersion which can be prepared by various methods has many advantages. However, despite numerous studies which have been carried out, limitations for commercializing these products remain to be solved. For example, during the manufacturing process or storage, amorphous form of solid dispersion can be converted into crystalline form. That is, the dissolution rate of solid dispersion would continuously decrease during storage, resulting in a product of no value. To resolve these problems, studies have been conducted on the effects of excipients. In fact, modification of the solid dispersions to overcome these disadvantages has progressed from the first generation to the recent third generation products. In this review, an overview on solid dispersions in general will be given with emphasis on the various manufacturing processes which include the use of polymers and on the stabilization strategies which include methods to prevent crystallization.

Key words − Solid dispersion, Polymeric carrier, Bioavailability, Crystallization, Stabilization

With the discovery of many novel drug candidates, the importance of finding appropriate formulations and treatment routes for these bioactive entities is emphasized more than ever. There are various factors that need to be considered to make these drugs into the right dosage formulation. The initial developmental direction is whether the drug has hydrophilic or hydrophobic properties because drugs have to have an adequate effect at the target site. These properties are important in terms of stable delivery until they reach the exact target site.

The focus of this review will be on oral drug formulations which need to pass through the gastrointestinal site while being transported to target. As a matter of fact, most of the newly-discovered drugs have poor water solubility (van Drooge, 2006; Vasconcelos and Sarmento et al., 2007). Since the gastrointestinal membrane has lipophilic components, these hydrophobic drugs can easily permeate through the gastrointestinal membrane (Gardner, 1997; Streubel, 2006). However these drugs lack an essential factor for enhancing drug's bioavailability which is water solubility in the hydrophilic gastrointestinal fluid (Ohara, 2005; Desai, 2006; Streubel, 2006; Vippagunta and Wang et al., 2007). Reducing the drug particle size or modifying the drug's structure to become more water soluble is a few examples of methods that can be utilized to make the drug more soluble in the GI fluid. However, altering the drug particle itself carries obvious limitations which are inadequate for enhancement of bioavailability. Therefore, additional physical changes including control of drug release from their formulations should be taken into consideration.

Solid dispersion is one of the most successful strategies for improving the drug release profile. A broad range of newly discovered drugs are formulated using this solid dispersion technique. Moreover, several useful carriers which have been discovered make solid dispersion one of the most efficient pharmaceutical formulations. Therefore, despite the remaining problem of stability, the development of polymers and surface active carriers are revealing promising results in improving the dispersion formulations. An overview on solid dispersions in general will be given in this review with emphasis on the various manufacturing processes and on the stabilization strategies.

Definition of Solid Dispersion

Solid dispersion, as implied in its name, refers to the solid state where one substance is dispersed into another material. The substances can be mixed completely or partially, containing several phases. In general, solid dispersion is defined as

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the dispersion of one or more active ingredient in a carrier or matrix at solid state (Chaudhari.P.D., 2006). When solid dispersion is used as a pharmaceutical formulation, the active ingredient from the former written definition would be the bioactive drug and the matrix would be the solid material that disperses the drug in itself. In most cases, the drugs have low water solubility. Therefore, we can define solid dispersion with more pharmaceutically detailed meaning as the mixture of hydrophilic matrix and the hydrophobic drug (Chiou and Riegelman, 1971; Dhirendra and Lewis et al., 2009). The drug in solid dispersion can be dispersed molecularly, in amorphous particles, or in crystalline particles. The matrix can also be in crystalline or amorphous state. The purpose of making hydrophobic drugs into solid dispersion formulation is to disperse the hydrophobic drug into the hydrophilic matrix so that the hydrophilic matrix can melt prior to the drug in the gastrointestinal fluid. The drug dispersed in the matrix can then be saturated in the gastrointestinal fluid with rapid dissolution rate when the solid dispersion drug is taken orally. Drug saturation in GI fluid can help improve the efficiency of drug absorption through the GI membrane.

Several decades ago, solid dispersion was considered as eutectic mixtures of drugs with highly water-soluble carriers by melting of their physical mixtures (Serajuddin, 1999; Chaudhari.P.D., 2006; Vippagunta and Wang et al., 2007; Liu, 2008). However, it was demonstrated later by Goldberg that the drug can be molecularly dispersed partially in the matrix (Goldberg and Gibaldi et al., 1965; Goldberg and Gibaldi et al., 1966; Liu, 2008). As solid dispersion techniques developed, materials used as carriers have been changed from crystalline ones such as urea or sugar to amorphous carriers including polymers. Thus the generally used form of solid dispersions became the amorphous solid dispersions with the drug being supersaturated in the polymer matrix (Vasconcelos and Sarmento et al., 2007). Recently, carriers which have surface activity like surfactants, and those having self-emulsifying property are being used. These surface-active agents, at their low concentrations, adsorb onto the surfaces or interfaces of a system and alter the surface/interfacial free energy and surface/interfacial tension. That is, these surface active carriers commonly possess both polar and non-polar regions in the same molecule, being amphipathic in nature. Therefore, in order to prevent the crystallization of commonly-used amorphous solid dispersions, research on formulations using surfactant carriers with amorphous polymer for dispersion of drugs are actively being pursued (Corrigan and Healy, 2002; Chaudhari.P.D., 2006; Vasconcelos and Sarmento et al., 2007).

The Classification of Solid Dispersions

First generation

The first generation solid dispersions were made using crystalline carriers. These form thermodynamically stable crystalline solid dispersions, which release the drugs slowly (Vasconcelos and Sarmento et al., 2007). The first reported solid dispersions were made by Sekiguchi and Obi in 1961 (Sekiguchi and Obi et al., 1964). The strategy they used for the preparation was forming eutectic mixtures which are binary systems consisting of drug and carrier. Eutectic mixtures are formed when the drug and carrier are homogeneously mixed in melted state, but they become immiscible when cooled and crystallized. Eutectic point refers to the drug crystallizing out simultaneously only in the specific composition. The melting point of mixture at the specific composition is lower than at any other points. Some scientists argue that lowering of melting point is a direct evidence of interaction between the drug and the carrier in the molecular level (Liu, 2008). In the eutectic point, the mixture consists of fine crystals of two components. Most of the time, the drug has negligible water solubility and the carrier is highly water soluble. However, when it is dissolved in an aqueous medium, the carrier part will dissolve quickly and, the drug part is released in the form of fine crystals. The fast release gives eutectic solid dispersion a rapid dissolution rate of drug. The large surface area of these small size particles results in better wettability, which is why eutectic solid dispersions improve bioavailability. Polyethylene glycols (PEG), urea and polyoxyethylene-polyoxypropylene (Pluronic®) form good pharmaceutical-property eutectic mixtures (Leuner and Dressman, 2000).

There are two kinds of solid solutions. One is continuous solid solution, in which the two phases are miscible in every proportion. This type of solid solution has not been applied to pharmaceutical products. The other one is discontinuous solid solutions in which the solubility of each component is limited. In this case, there are two things to consider. One is solubility to each other and the other is dose of the drug. If the solubility of the drug in the carrier is 1% and dose of the drug is 100 mg, the total amount of dosage form is 10000 mg (carrier takes up 99%). It is much higher than the upper limit of the one-time-dose and thus has no marketability. So Goldberg suggested that the term solid solution should only be applied when the mutual solubility of the two components exceeded 5% for practical reason (Goldberg and Gibaldi et al., 1966).

In most cases, pharmaceutical solid solutions are amorphous than crystalline. Although there are some methods reported for making crystalline solid solutions like crystal inclusion and

crystal doping technique, crystalline solid solution has not been widely used. Amorphous solid solutions have faster dissolution rate. These molecularly dispersed systems have very large effective surface area. In the case of felodipine-PVP system, hydrogen bond between felodipine and PVP enhance drug dissolution (Karavas and Ktistis et al., 2006). This effect minimizes molecular mobility so that the conversion of amorphous drugs to crystalline forms is delayed. Consequently, solid solutions also have good physical stability.

Second generation

In the 1960s, it was reported that amorphous solid dispersions were more effective than crystalline solid dispersions because of the thermodynamic stability (Chiou and Riegelman, 1969; Simonelli and Mehta et al., 1969). Therefore the second generation solid dispersions contain amorphous carriers which are mostly polymers (Vilhelmsen and Eliasen et al., 2005).

Polymeric carriers are divided by its origin. One is fully synthetic polymers, which includes povidone (PVP) (Simonelli and Mehta et al., 1969; Lloyd and Craig et al., 1999; Hasegawa and Hamaura et al., 2005; Karavas and Georgarakis et al., 2006; Pokharkar and Mandpe et al., 2006; van Drooge and Braeckmans et al., 2006; van Drooge and Hinrichs et al., 2006; Yoshihashi and Iijima et al., 2006), polyethyleneglycols (PEG) (Chiou and Riegelma.S, 1970; Guyot and Fawaz et al., 1995; Prabhu and Ortega et al., 2005; Yao and Bai et al., 2005; Urbanetz, 2006) and polymethacrylates (Ceballos and Cirri et al., 2005; Huang and Wigent et al., 2006). The other is natural product based polymers, which is composed of cellulose derivatives like hydroxypropylmethylcellulose (HPMC) (Ohara and Kitamura et al., 2005; Won and Kim et al., 2005; Konno and Taylor, 2006), ethylcellulose (Ohara and Kitamura et al., 2005; Desai and Alexander et al., 2006; Verreck and Decorte et al., 2006) or hydroxypropylcellulose (Tanaka and Imai et al., 2005; Tanaka and Imai et al., 2006) or starch derivates, like cyclodextrins (Rodier and Lochard et al., 2005; Garcia-Zubiri and Gonzalez-Gaitano et al., 2006).

Amorphous solid dispersions can be classified into solid solutions, solid suspensions or a mixture of both (van Drooge and Braeckmans et al., 2006; van Drooge and Hinrichs et al., 2006). In amorphous solid solutions, the drug and carrier are fully soluble with each other, making a homogeneous mixture. The use of polymers makes the crystalline drug dissolved in them, and thus they exist in one phase (van Drooge and Hinrichs et al., 2006). Amorphous solid suspensions are made when the drug has limited carrier solubility or are of very high melting points (Chiou and Riegelman, 1971). They do not have homogeneous structure; rather, they consist of two phases. Amorphous drug particles are dispersed in polymeric carriers. In all cases, drugs are in their supersaturated state which is a result of forced solubilization (Vilhelmsen and Eliasen et al., 2005; Tanaka and Imai et al., 2006; Urbanetz, 2006). In second generation solid dispersions, the carrier materials provide the drug with wettability and dispersibility, and thus the carrier dissolution pattern dominates the drug release profile (Damian and Blaton et al., 2000; Karatas and Yuksel et al., 2005).

Third generation

In the third generation, solid dispersions include additional surface active properties. Surface active carriers are introduced and dissolution profiles are improved (Vasconcelos and Sarmento et al., 2007). In case of carriers not having the surface active property, surfactant is added. Although this system is also third generation solid dispersions, binary systems are more common than ternary systems. The typically used surfactants as carriers for solid dispersions are inulin (van Drooge and Hinrichs et al., 2006), inutec SP1 (Van den Mooter and Weuts et al., 2006), compritol 888 ATO, gelucire 44/14 (Chauhan and Shimpi et al., 2005; Karatas and Yuksel et al., 2005) and poloxamer 407 (Majerik and Charbit et al., 2007). The surface activity which prevents nucleation and agglomeration (Pouton, 2006) may improve stability physically and chemically.

Advantages of Solid Dispersion

The drugs used in solid dispersions which are generally hydrophobic can become sufficiently soluble with enhanced dissolution rate than in other formulations due to the unique properties of solid dispersion which will be mentioned below. One method for improving bioavailability of the drug is to solubilize drugs in oral formulations with the appropriate solvents. However, the main problem of this method is the amount of the solvents required to dissolve the poorly water-soluble drug, which is in general too much for one dose

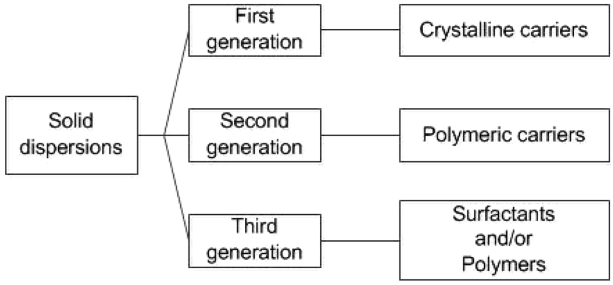

Figure 1. Classification of solid dispersions.

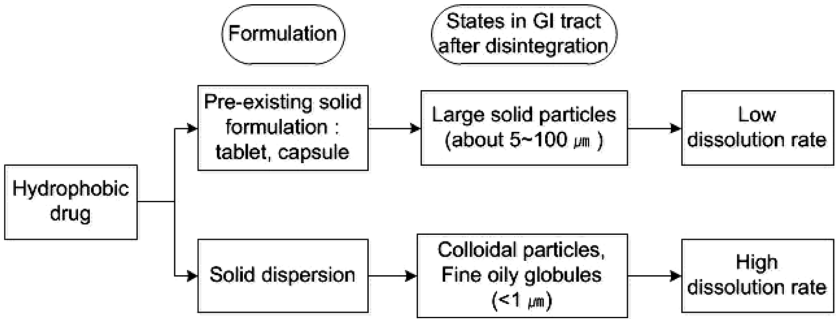

Figure 2. Advantage of solid dispersions due to particle size reduction.

amount. On the other hand, the advantage of solid dispersions is that the drug need not be fully solubilized in the excipient matrix. Solid dispersion is in the solid state, which disperses the drug already in its matrix. As shown in Figure 2, there are certain advantages that solid dispersion have compared to other solid drugs including tablets or the capsules (Serajuddin, 1999; Joshi and Tejwani et al., 2004; Liu, 2008). The minimum particle size that can be formed in pre-existing formulations (tablets or capsules) is only 5 μm (Serajuddin, 1999). There are limitations in making size reduction of pre-existing tablet or capsule formulations. In general, it is difficult to make particle size of drug in capsules or tablets below 2~5 μm (Serajuddin, 1999; Leuner and Dressman, 2000; Rasenack and Muller, 2004; Muhrer and Meier et al., 2006; Karavas and Ktistis et al., 2006; Pouton, 2006; Vasconcelos and Sarmento et al., 2007; Liu, 2008). However, in the case of solid dispersion, drug is molecularly dispersed in the dissolution matrix (Leuner and Dressman, 2000; Bikiaris, 2005; Vasconcelos and Sarmento et al., 2007). Some portion of the solid dispersion-formulated drug dissolves immediately upon contact with the gastrointestinal fluid to saturate the gastrointestinal fluid (Liu, 2008). These drugs are presented as supersaturated solutions after system dissolution (Goldberg and Gibaldi et al., 1966; Leuner and Dressman, 2000; Karavas and Ktistis et al., 2006; Van den Mooter and Weuts et al., 2006). Supersaturated drug in the gastrointestinal fluid makes more rapid absorption possible, consequently helps the absorption of the drugs. The supersaturated drug can precipitate in gastrointestinal fluid, and excess drug can precipitate out as fine colloidal particles or oily globules of submicron size (<1 μm) which can improve bioavailability by accelerating the dissolution rate (Serajuddin, 1999; Leuner and Dressman, 2000).

Also, drug particles dispersed in the matrix in the form of solid dispersion have higher porosity than in other formulations. This increased porosity makes the drug released more rapidly, improving the bioavailability of drug more efficiently (Ghaderi and Artursson et al., 1999; Vasconcelos and Costa, 2007). By changing the polymers in the solid dispersions, the degree of porosity can be changed (Ghaderi and Artursson et al., 1999). If the polymer structure is reticular, which means a web formation, its porosity would be smaller than that of a linear polymer resulting in faster drug release rate in linear polymer compared to that of reticular polymer. However, in general, regardless of the structure of the polymer used in solid dispersion, that is whether linear or reticular, solid dispersions with polymers have bigger porosity than in other formulations, resulting in more rapid release with higher bioavailability.

One way of improving bioavailability of the drug is to form pro-drugs. However, if the salt form of a drug is needed, only weakly basic or weakly acidic compounds can be used for this purpose (Serajuddin, 1999; Karavas and Ktistis et al., 2006). However, since solid dispersion can easily exert biological effects in our body by simply dispersing the drug in the matrix with surface activity using carriers, prodrug form need not be prepared. In addition, by selectively using different polymers or carriers according to the demanded characteristics or objects, different types of solid dispersions can be prepared (Cutler and Howes et al., 2006; Fukami and Yonemochi et al., 2006) Yoshihashi, 2006; Majerik, 2007). Using carriers with surface activity such as cholic acid or bile salt, the wettability of drugs in gastrointestinal fluid can be markedly improved (Leuner and Dressman, 2000; Kang and Lee et al., 2004; Karavas and Ktistis et al., 2006; Pouton, 2006). This is true even with simple carriers which have no surface activity like urea or cellulose (Sekiguchi and Obi et al., 1964).

The most remarkable property of second generation solid dispersions is the change of drug form from crystalline to amorphous. It was demonstrated that drugs with low water solubility have higher solubility when they are in amorphous state rather than in crystalline state (Lloyd and Craig et al., 1999; Pokharkar, 2006). Theoretically, certain amount of energy is demanded for breaking up the crystal lattice during the dissolution process if the drug is in its crystal state. However, amorphous drugs do not need such energy (Ghaste et al.,

2009), making drug more easily released (Taylor and Zografi, 1997). This improved drug release rate ultimately promotes drug's bioavailability, making solid dispersions more ideal for administrating hydrophobic oral drugs.

Methods for Preparing Solid Dispersions

There are several methods for preparing solid dispersions and thus choosing the suitable method is important. The three major methods include: Melting methods, Solvent evaporation methods, and Melting solvent methods (Vilhelmsen and Eliasen et al., 2005).

Melting method

The initial solid dispersions consisting of drug within urea as a carrier were created by the melting method (Sekiguchi and Obi, 1961). In melting or fusion method, the physical mixture of the drug and carrier is heated until melted after which the molten mixture is cooled and solidified by processes including ice-bath stirring, cooling on stainless steel thin layer by flowing air or water, plunging in liquid nitrogen, putting on petri dishes inside a dessicator (Chiou and Riegelman, 1969; Owusu-Ababio and Ebube et al., 1998; Yao and Bai et al., 2005; Pokharkar and Mandpe et al., 2006). The last step is crushing, pulverizing and sieving the mixture for ease of handling (Owusu-Ababio and Ebube et al., 1998).

However, the melting method has several serious problems. Because of high heating temperature, some drugs and even carriers can be degraded (Serajuddin, 1999). During cooling, the drug-carrier mixture miscibility can alter and phase separation can occur (Save and Venkitachalam, 1992). The major limitation of the melting method is that if drug and carrier are not compatible or if they are not mixed thoroughly, solid dispersion may not be homogeneous (Timko and Lordi, 1984).

To overcome these problems with the original melting method, several modifications have been introduced including the hot melt extrusion (HME). Compared to the conventional melting methods, the difference is in using an extruder (Breitenbach, 2002). A melt extruder consists of an opening feed port, a heated barrel which has screw and an exit port. As the physical mixture of drug and carrier enter through the feed port, it is conveyed to the heated screws at constant rate by a motor, and then transformed into homogeneous mixture like fluid by the high shear of screws. Finally the molten mixture which is the solid dispersion is extruded through the exit port which consists of die opening, and then by additional rolls, cut into dosage forms (Breitenbach, 2002). However, like in the original melting methods, miscibility of drug and carrier, and also high temperature in extruder are the problems (Forster and Hempenstall et al., 2001). Thus, carriers should be carefully selected (Forster and Hempenstall et al., 2001). PVP, HPMC, HPMCAS, PEO, and Eudragit EPO are some of the carriers used in manufacturing solid dispersions of indomethacin (Forster and Hempenstall et al., 2001), itraconazole (Verreck and Six et al., 2003), nifedipine (Li and AbuBaker et al., 2006), and many other drugs. The advantages of the HME methods include continuous production applicable for large scale manufacturing. Besides, manufactured solid dispersions by HME are easier to handle than those from the original melting method because the exit port which consists of the die opening shape makes it possible to produce the solid dispersions into dosage form such as tablets and capsules (Dhirendra and Lewis et al., 2009).

Meltrex^{TM} is one of the melting methods. The important

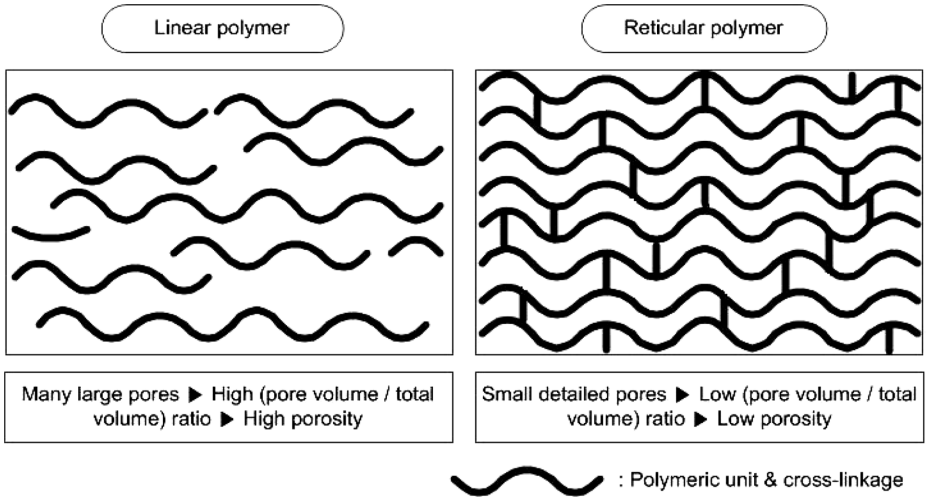

Figure 3. Advantage of solid dispersions containing polymers with higher degree of porosity.

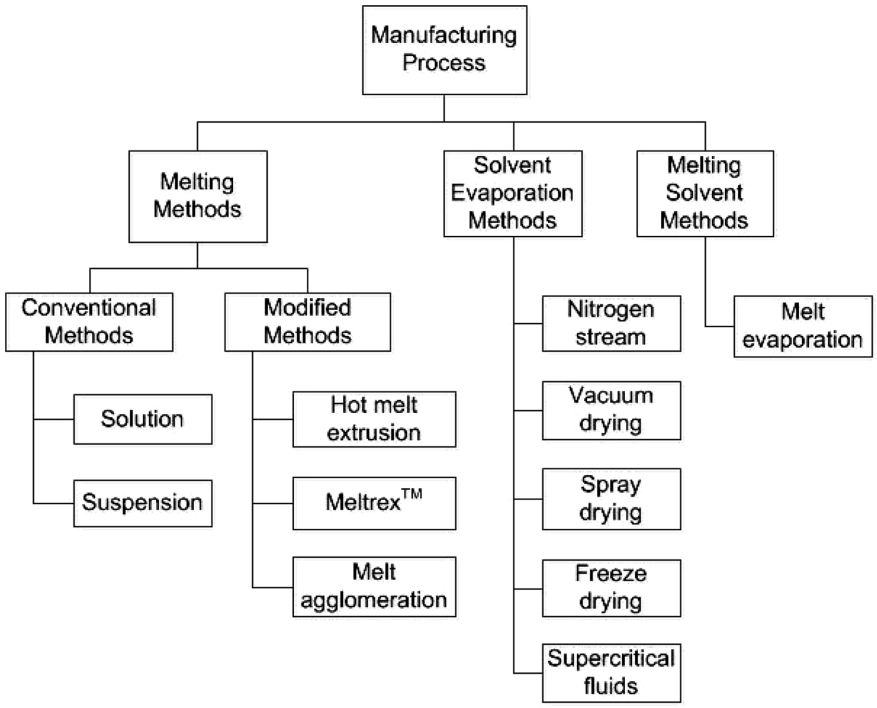

Figure 4. Manufacturing processes of solid dispersions.

components in the Meltrex™ are the twin screw extruder and two independent hoppers. These elements reduce staying time of the mixture in the extruder and permit a continuous process. In addition, because of the broad temperature range, the drug and carrier can avoid thermal problems. The melt agglomeration method, on the other hand, can produce stable solid dispersion wherein the binder acts as the carrier using rotary processor (Vilhelmsen and Eliasen et al., 2005). This processor might be favorable for the high melt agglomeration because it is easier to handle on the temperature range and a high concentration binder can be integrated into the agglomerates (Vilhelmsen and Eliasen et al., 2005). In melt agglomeration, the type of binder, method of preparing and particle size not only influence dissolution rates of solid dispersions, but also affect agglomerates formation, growth and size (Seo and Schaefer, 2001).

Solvent evaporation method

In the solvent evaporation method, the drug and carrier are first solubilized in a volatile organic solvent. The next step in this method is evaporation of solvent resulting in manufacturing of a solid dispersion (Rodier and Lochard et al., 2005). The major merit of this method compared to the melting method is that thermal degradability of the drug and carrier can be inhibited because volatile organic solvent is easily evaporated at relatively low temperatures (Won and Kim et al., 2005). Nevertheless, there are disadvantages to this method which is the difficulty in evaporating the volatile solvents completely. The residual solvent presented in solid dispersion after drying may cause toxicity (Dhirendra and Lewis et al., 2009). Moreover, selecting the suitable volatile solvent is difficult since phase separation, especially crystallization, may occur during evaporation of solvent.

Methods for solvent evaporation can be sub-classified as the following; using nitrogen stream (N_2 gas), vacuum drying, spray drying, freeze drying (lyophilization), and supercritical fluids (SCF) (Dhirendra and Lewis et al., 2009). In evaporation step, nitrogen gas is generally used. Because it is inert gas and has high vapor pressure, organic solvents are evaporated on the flow of nitrogen gas. Vacuum drying is often used in the solvent evaporation method. A mixture of the drug and carrier is evaporated in a vacuum. Then, the manufactured solid dispersion is kept in vacuum desiccators until the residual solvent is extirpated (Langer and Holtje et al., 2003). Spray drying is used to evaporate the volatile organic solvent with frequency. In spray drying, to evaporate solvent, the mixture of drug and carrier is sprayed into heated air flow (Chauhan and Shimpi et al., 2005). The advantage of spray drying method is its prompt evaporation of solvent and formation of solid dispersion. On this account, phase separation can be avoided during evaporation. Moreover, solid dispersions by spray drying are often manufactured in amorphous state although it may be partially

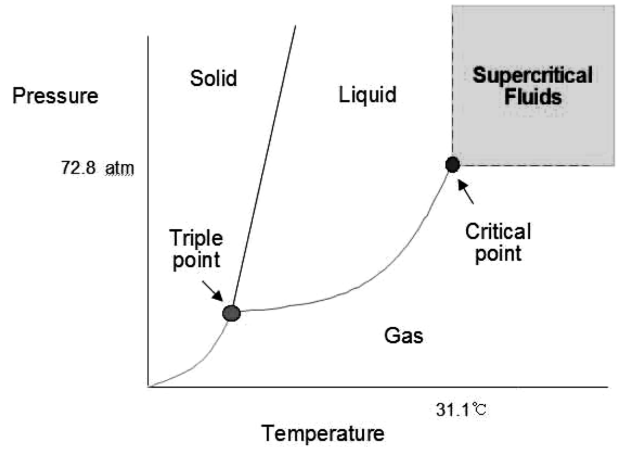

Figure 5. Supercritical fluid of carbon dioxide (CO_2).

changed to the more stable crystalline state (Paradkar and Ambike et al., 2004; Weuts and Kempen et al., 2005). The freeze drying method, otherwise known as lyophilization, contains the following step: the mixture of drug and carrier is soaked in liquid nitrogen until the solvent is completely frozen (van Drooge and Braeckmans et al., 2006). The merit of this method is nominal thermal problems. What is more important one is that possibility of phase separation is minimized (Leuenberger, 2002). However, because the freezing point of most organic solvents is quite low, it is difficult to sublimate the organic solvent completely (Dhirendra and Lewis et al., 2009). On the other hand, supercritical fluid method is also often used as the solvent evaporation method. Supercritical fluid (SCF) is a state where the boundaries between liquid and gas is collapsing. This character is shown above the critical point containing the critical temperature and the critical pressure. In the supercritical region, in other words, above the critical point, SCF has a characteristic of liquid and at the same time that of gas. Above all, carbon dioxide (CO_2) is the most frequently used because its critical temperature and pressure are relatively low (31.1°C, 72.8 atm) while being inactive with little toxicity (Majerik and Charbit et al., 2007).

In the SCF method, supercritical CO_2 is sprayed into the mixture of drug and carrier in the extracter through a nozzle. The mixture is dissolved in SCF. And then, as the pressure decreases in the extracter, the solid dispersion is precipitated rapidly (Won and Kim et al., 2005). This technique is known as Rapid Expansion of Supercritical Solution (RESS) (Subramaniam and Rajewski et al., 1997). Using RESS method improves dissolution rate of hydrophobic drugs in solid dispersions (Sethia and Squillante, 2002; Gong and Viboonkiat et al., 2005), and reduces the particle size to micro- or nanoparticle (Sethia and Squillante, 2002; Turk and Helfgen et al., 2002; Won and Kim et al., 2005; Majerik and Charbit et al., 2007), as a result improving the bioavailability of poorly water-soluble drugs (Sethia and Squillante, 2002; Won and Kim et al., 2005; Majerik and Charbit et al., 2007).

In addition to the above mentioned methods, there are others that are modified procedures which include the Gas Anti-Solvent technique (GAS), Precipitation from Gas Saturated Solutions (PGSS), Precipitation with Compressed Anti-Solvent (PCA), Supercritical Anti-Solvent (SAS), Aerosol Solvent Extraction System (ASES) and Solution Enhanced Dispersion by Supercritical fluids (SEDS) (Dhirendra and Lewis et al., 2009).

Melting solvent method

The melting solvent method utilizes both the melting and evaporation steps of the melting method and solvent evaporation method, and thus encompasses the advantages of both methods (Goldberg and Gibaldi et al., 1966). In this method, drugs are dissolved in suitable solvent, and followed by incorporating the solution into the molten PEG. And then solvent is evaporated, thereby easily incorporating the drugs into PEG without loss of its solid property.

Polymeric Carrier Used in Solid Dispersion

Polyethylene glycol (PEG)

Polyethylene glycol is the polymer of oxidized ethylene and is usually transparent or white solid. It is widely used as a mixture with other substances due to its unique properties. Generally, it is expected to obtain the desired form, viscosity, melting point, and water-solubility by mixing the substance with PEG. There is no substantial limit in the number of the polymeric units to be polymerized. In the chemical formulation of $OHCH_2$ $(CH_2OCH_2)_n$ CH_2OH, by changing the number n of the polymerized units, it is possible to make drug having desired properties. In particular, for poorly water-soluble drugs, PEG can give improved hydrophilicity, thus giving rise to higher bioavailability. PEG commonly used in solid dispersions generally are of molecular weight of 1500~20000 (Leuner and Dressman, 2000). By increasing the molecular weight of PEG, the viscosity from its fluid state to hard crystal form can be adjusted. Polyethylene glycol not only has good water solubility, but it also has good solubility in many organic solvents. Since various organic solvents are essentially used in the preparation process, PEG can make the preparation much easier. It is also possible to improve drugs' wettability using this amphipathic solubility (Okonogi and Yonemochi et al., 1997) as well as possible to change melting points by adjusting

the molecular weight of the polyethylene glycol. In other words, if the adequate molecular weight of polyethylene glycol is chosen, the solid dispersion with lower melting point can be prepared. Therefore, some preparation methods such as melting method which include the process of heating the mixture of drug and polymer to its melting point can become more applicable (Price, 1994; Leuner and Dressman, 2000).

However, in the case of using polyethylene glycol with a too low molecular weight or if PEG interacts with certain drugs, solid dispersion can become too soft (Shah and Chen et al., 1995). It is also important to select the adequate preparation method. For example, PEG might become too unstable during solid dispersion preparation process using hot melt method (Dubois and Ford, 1985). In terms of toxicity, PEG with high molecular weight has no such risk in its use. However it was demonstrated that, as the molecular weight decreases, the chance for the polyethylene glycol to have its own toxicity can become slightly higher (Price, 1994).

Polyvinylpyrrolidone (PVP)

Polyvinylpyrrolidone is the polymerized product of vinylpyrrolidone and generally has molecular weight ranging from about 2,500 to 3,000,000. The structure consists of the polymeric unit of lactam with an internal amide bond which is polar and of a highly water soluble functional group making PVP highly hydrophilic. This water solubility can improve dispersed drug's wettability as is the case of PEG improving the drug's bioavailability by making the dissolution rate faster (Itai and Nemoto et al., 1985). Moreover, PVP with its internal amide bond has similar structure with protein as a whole, which means it has high bioaffinity. Therefore, oral bioavailability would be improved by taking solid dispersions prepared with PVP (Leuner and Dressman, 2000; Ning and Sun et al., 2011). Also, as is the case with PEG, PVP has high solubility in both water and broad ranges of organic solvents. Therefore the solvent method is adjustable to solid dispersion using PVP.

PVP is also able to prevent crystallization of amorphous drug through nucleation. By heightening the nucleation kinetic barrier, the nucleation rate can be slowed down (Konno and Taylor, 2006). Because of these advantages as mentioned above, PVP is the most commonly used polymer as carrier in making solid dispersions. The toxicity of PVP is not problematic at all in per oral solid dispersion formulations. However, it has been reported that granuloma occurs in the case of PVP being intramuscularly injected (Walking, 1994). Yet, the possibility for PVP to be absorbed in the gastrointestinal tract is low when patients take solid dispersion drug using PVP per oral. Because PVP in general has comparatively large molecular weight, PVP cannot be absorbed in the gastrointestinal membrane, and thus not able to cause toxic effect in the human body (Leuner and Dressman, 2000).

Polyvinylalcohol (PVA), crospovidone (PVP-CL), polyvinylpyrrolidone-polyvinylacetate copolymer(PVP-PVA)

The three polymers, PVA, PVP-CL, and PVP-PVA, all belong to the polyvinyl group. The dissolution rate is shown to be about 20 times faster in solid dispersions when PVA is added as a carrier (Suzuki and Sunada, 1998). Morever, solid dispersions using PVP-PVA copolymer showed drug dissolution rate to be 25 times faster resulting in higher bioavailability than solid dispersion without the carrier (Kondo and Iwao et al., 1994). As PVA and PVP-PVA copolymer are able to dissolve well in water, both can improve drug's bioavailability in the same way as PVP or PEG. On the other hand, in case of crospovidone, it swells rather than dissolves when it is dispersed in water. However, even though crospovidone cannot dissolve in water well, it can improve drug's release rate while preparing the solid dispersion (Shin and Oh et al., 1998). High ratio of PVP-PVA to drug can increase viscosity of near surface to which the drug dissolves bringing about a delay in the time needed for the drug to be released through the diffusion layer (Zingone and Rubessa, 1994). Therefore, if PVP-PVA is added in a much higher ratio than the drug while solid dispersion is prepared, it can reduce the drug's release rate.

Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are polymers of acrylic acid and methacrylic acid. They are also used as polymeric carrier in making solid dispersion. For the same purpose, derivatives with various simple functional groups to these polymers are frequently used. If the drug can be coated with these polymers or their derivatives, it is possible to control the drug release rate according to their molecular weight (Shukla, 1994; Suzuki and Miyamoto et al., 1996).

Urea

Urea, different from the former polymers, is a substance which already exists in our body. As a pre-existing substance which is the ultimate form just before protein product is excreted after metabolism, it has less risk for its toxic effect than other substances. This was also the reason for it to have been used as a matrix since the 1st generation of solid dispersion started to be developed (Sekiguchi and Obi, 1961; Sekiguchi and Obi et al., 1964). Also, it was one of the first materials being researched for improving the bioavailability of solid dispersions (Sekiguchi and Obi, 1961; Goldberg and

Gibaldi et al., 1966). Similar to most of the former polymers, urea has high solubility to water and also to various organic solvents. However, although there is obvious improvement in drug's dissolution rate if urea is used as carrier (Okonogi and Oguchi et al., 1997), its effectiveness in improving the drug release rate is no better than with other polymers such as PVP or PEG.

Sugar, polyols and their polymers

Sugar and polyols have good water solubility as there are many hydroxyl groups in their structure. As they already exist in our body and are used through metabolism, sugars can be considered as having no severe toxicity. However, they are used less as a carrier than the other substances in preparing solid dispersion because they have considerably high melting point, making preparation of solid dispersion by several major methods difficult. For instance, some preparation methods include the process of making mixture of matrix and drug with quite high temperature. At this condition of high temperature, there is high possibility for the drug or the whole structure of the drug to be destroyed. Also, while sugar is highly soluble in water due to its hydrophilic functional groups, it has poor solubility in most of the organic solvents. Yet, there are a few drugs which were proven to show improved drug release property when using sugar or polyols as carrier (Ali and Gorashi, 1984; Jachowicz, 1987; Okonogi and Oguchi et al., 1997).

Emulsifiers

Emulsifying agents improve drug bioavailability through two mechanisms. First of all, they can improve drug's wettability which can increase drug dissolution rate, thereby improving bioavailability. Another mechanism is by improving drug's solubility. Most of the drugs used in solid dispersion are lipophilic, so it is useful to improve their wettability and solubility. For this purpose, bile salt such as cholic acid, deoxycholic acid, lithocholic acid and their derivatives are frequently used as emulsifying agents (Stoll and Bates et al., 1969; Kim and Jarowski, 1977).

Organic acids and their derivatives

Organic acids such as nicotinamide, citric acid, succinic acid and their derivatives with varying functional groups can be used as carriers of solid dispersions. They help improve drug's bioavailability by accelerating the drug's release rate. There are several researches which identified that drug release rate can be increased 20 times if these organic acids are used with polymeric carriers such as HPMC or PVP (Goldberg and Gibaldi et al., 1966; Chiou and Riegelman, 1969; Suzuki and Sunada, 1997; Suzuki and Sunada, 1998).

Other factors to be considered

There are several factors to be considered when utilizing the above mentioned substances as carrier for solid dispersion of

Table I. *Examples of polymers used in solid dispersions*

	Polymer chain length	Drug/Polymer system	References
PEG	PEG 4000~6000	griseofulvin, oxazepam, piroxicam, zolpidem, glyburide, carbamazepine, nifedipine, norfloxacin, carbamazepine, ketoprofen, phenytoin, ursodeoxycholic acid, fenofibrate, prednisolone	Chiou and Riegelman 1969 ; Ali and Gorashi 1984; Ford, A.F. et al. 1986; Jachowicz 1987; Sjokvist, Nystrom et al. 1992; Fernandez, Margarit et al. 1993; Margarit, Rodriquez et al. 1994; Sheu, Yeh et al. 1994; Shah, Chen et al. 1995; Fawaz, Bonini et al. 1996; Gines, Arias et al. 1996; Lin and Cham 1996; Lo and Law 1996; Okonogi, Yonemochi et al. 1997; El-Zein, Riad et al. 1998; Khan and Zhu 1998; Perng, Kearney et al. 1998; Mura, Faucci et al. 1999; Trapani, Franco et al. 1999
PVP	PVP 2500~50000	griseofulvin, sulphathiazole, hydrochlorothiazide, piroxicam, mefenamic acid, azapropazone, glafenin, flotafenin	Mayersohn and Gibaldi 1966 ; Simonelli, Mehta et al. 1969; Corrigan, Timoney et al. 1976; Kassem, Zaki et al. 1979; Ramadan, Abd El-Gawad et al. 1987; Doherty and York 1989; Kearney, Gabriel et al. 1994; Torrado, Torrado et al. 1996; Yagi, Terashima et al. 1996; Tantishaiyakul, Kaewnopparat et al. 1999
PVA	PVA 10000~40000	nifedipine, HO-221	Kondo, Iwao et al. 1994 ; Zingone and Rubessa 1994; Moneghini, Carcano et al. 1998; Suzuki and Sunada 1998

PEG, Polyethylene glycol ; PVP, Polyvinylpyrrolidone ; PVA, Polyvinylalcohol

drug. Most important factors are the polymer chain length, drug/polymer ratio and individual combinations of each drug with various polymers. Table 1 shows the detailed conditions that have been studied when using key polymers in solid dispersion.

The polymer chain length is primarily an essential factor to be considered when using these polymers. As many studies show, the release rate is inversely proportional to the chain length of the polymers (Ford et al., 1986). Of course, sometimes, increase in viscosity due to the increased molecular weight can alter this general tendency. However, control of the chain length is still very important since the core unique characteristic of polymers is that the number of polymeric units to be polymerized.

Drug/polymer ratio is also very important because it directly affects the performance of a solid dispersion. If the ratio of drug to polymers is too high, molecularly dispersed state of the drug could change into crystalline state. On the other hand, if the carrier has much higher ratio to drug, than crystallization of drug can be prevented to some extent, which leads to induction of solubilization and rapid release.

Also, the effect of polymers to the performance of solid dispersions would be different based on the kinds of drug. There would be some exceptional drugs that do not follow the general expected behaviors or actions. So in these cases, detailed factors for each drug should be considered based on previous findings. As each drug has unique characteristics, there might be some modifications when used with the polymers. Therefore, drug/polymer system should also be carefully considered when preparing solid dispersions.

Limits of Solid Dispersions

Despite the robust researches until now and the advantages revealed of solid dispersions, their application in the market is limited. Only few formulations have been commercialized (Dhirendra and Lewis et al., 2009). What limits the development of these solid dispersion formulations?

The methods themselves first of all are too expensive and difficult to carry out. In addition, solid dispersions may be degraded or the physicochemical properties of the drugs themselves and carriers may change during the manufacturing processes. Especially, in the melting methods, melting temperatures are very high, which could degrade drugs and carriers (Chiou and Riegelman, 1971). Also cooling and solidifying molten mixtures are difficult steps in manufacturing solid dispersions (Sekiguchi and Obi, 1961; Chiou and Riegelman, 1969). In solvent evaporation methods, the common volatile organic solvents which dissolve both the drugs and carriers rarely exist because usually, the drugs in solid dispersions are poorly water-soluble and the carriers are water-soluble. To dissolve the hydrophobic drugs, the volume of organic solvents are large and the amount of drugs relatively minimal. So, manufactured solid dispersions may have no effect on the patient, causing only side effects due to the residual solvents. In fact, the complete removal of volatile organic solvents from the mixture of drug and carrier during manufacturing solid dispersions is almost impossible (Serajuddin, 1999).

Furthermore, it is difficult to reproduce solid dispersions, because the physicochemical properties of manufactured solid dispersions vary a great deal by the manufacturing methods such as heating rate, heating temperature, holding time at high temperature, cooling conditions and rate, evaporation methods and rate, used solvent, drug and solvent ratios, carrier and solvent ratios, and particle size. For example, in preparing the solid dispersions of nifedipine and PEG 4000, PEG 6000, the state of nifedipine is amorphous when the molten mixtures were cooled quickly, but crystalline when cooled slowly. (Save and Venkitachalam, 1992).

Every formulation of pharmaceutical applications must be finally of constant dosage forms to survive the commercial market and be used clinically. Even though solid dispersions have been developed to regular dosage forms such as tablets and capsules (Serajuddin, 1999; Dhirendra and Lewis et al., 2009), it is difficult to incorporate the solid dispersions into constant dosage forms, because they are too soft, of poor flow and of low stability (Serajuddin, 1999). Rather, incorporated solid dispersions into the tablets dissolved quite slowly, and

Table II. *Examples of commercial applications of solid dispersion formulation*

Trade name	Drug company	Ingredient in solid dispersion	Efficacy
Hepcure	CJ Jeil-Jedang	Amorphous adefovir dipivoxil in solid dispersion	Hepatitis type B
Sporanox	Janssen /Johnson&Johnson	Itraconazole in HPMC and PEG 20000	Antifungal
Cesamet	Lilly	Nabilone in PVP	CINV (Chemotherapy induced nausea and vomiting)

dissolution rate continuously decreased for storage time of tablets (Ford and Rubinstein, 1980). Therefore, scale-up of the manufacturing processes also has been difficult (Serajuddin, 1999).

Above all things, the most noticeable limitation of solid dispersions is the stability of solid dispersions during processing or storage. Solid dispersions are relatively unstable physically and chemically. They may exist in supersaturated, amorphous phase or crystalline phase (Serajuddin, 1999) but only the crystalline state is stable. So, during storage, these phases will be converted into the more stable crystalline state. As a result, the dissolution rates of solid dispersions continuously tend to decrease with aging. For instance, the amorphous form of griseofulvin-PEG 6000 solid dispersion was converted into crystalline during storage and the dissolution rates decreased (Chiou, 1977). Not only drugs but carriers forming amorphous phase may convert into the more stable crystalline form. Especially, in humid conditions, this conversion of amorphous form into crystal accelerates (Andronis and Yoshioka et al., 1997).

These crystallizations are influenced on the manufacturing methods. For example, in melting methods, the cooling rates influence on crystallization. If the molten mixtures of drug and carrier are cooled slowly, the crystallization of solid dispersions is less serious during storage (Saers and Nystrom et al., 1993). About chemical instability, in some processes like melt extrusion and hot-melt encapsulation, drugs and excipients including carriers are exposed to high temperature. It is natural that certain reactive intermediates are produced, followed by excipient degradation. When PEG 400, a commonly used carrier, is oxidized, it generates formaldehyde (Bindra and Williams et al., 1994). Not only formaldehyde but also peroxides can arise from the degradation of polyoxyethylene surfactants under this condition (Frontini and Mielck, 1995; Bergh and Magnusson et al., 1998; Bergh and Shao et al., 1998). Thus it requires cautious monitoring of the stability of carriers as well as drugs in solid dispersions during storage.

Strategies to Overcome the Drawbacks of Solid Dispersions

To overcome the limits of solid dispersions for commercialized formulations, several attempts are being made. One of the most attractive trials is the development of surface active carriers, otherwise known as self-emulsifying carriers. The merit of these surface active carriers over non-surface active carriers is briefly explained in Figure 6.

If non-surface active carriers (Figure 6A) are used to manufacture solid dispersions, the drug-rich solid layers which are water-insoluble are formed on the surfaces of solid dispersion. In this case, the solid dispersion dissolves slowly and has relatively low bioavailability (Serajuddin, 1999). However, when surface active carriers (Figure 6B) which have self-emulsifying effects are used, the particles are formed from solid dispersions. These large surface areas of particles of solid dispersions improve the dissolution of poorly water-soluble drugs, and then advance the bioavailability of the drugs (Serajuddin, 1999). Various efficient surface active carriers that can improve the dissolution rates of solid dispersions are shown in Table 3.

One of the commonly used surface active carriers is poloxamers which are known by the trade names, Pluronics. Poloxamers which are copolymers containing polyoxypropylene chain with a hydrophobic center, and two polyoxyethylene chains which are hydrophilic on both sides. Due to this amphiphilic property, poloxamers are commonly used as surfactant. Gelucires are also frequently used as surface active carriers. Gelucires are polyethylene glycol (PEG) glycerides containing mono, di, triglycerides and mono, diesters of PEGs. In addition to amphiphilic property, they come in various

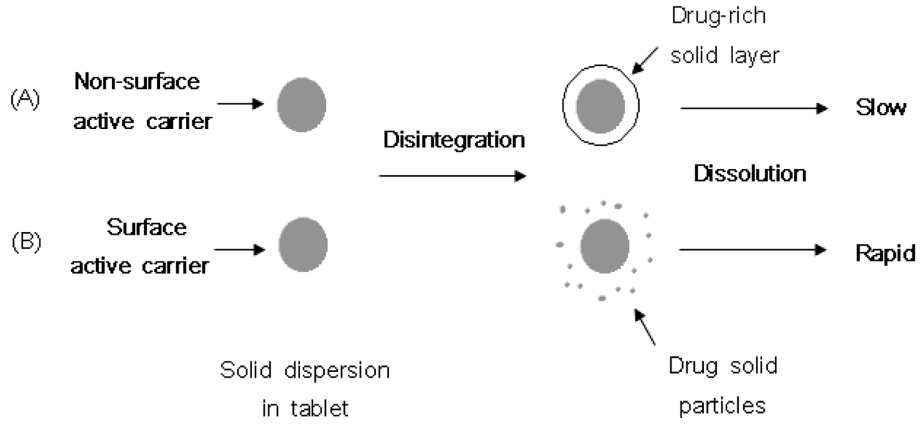

Figure 6. Relative dissolution rate of solid dispersions containing surface active carrier, compared to non-surface active carrier.

Table III. *Examples of surface active carriers improving dissolution rate of solid dispersions.*

Carrier	Drug	Reference
Poloxamer 188	Ibuprofen	Passerini and Albertini et al., 2002
Poloxamer 407	Nifedipine	Chutimaworapan and Ritthidej et al., 2000
Poloxamer 188 and Gelucire 50/13	Nifedipine	Vippagunta and Maul et al., 2002
Gelucire 44/14 or PEG 6000	Glibenclamide	Tashtoush and Al-Qashi et al., 2004
Gelucire 44/14 and Soya lecithin	Ubidecarenone	Pozzi and Longo et al., 1991
PEG 8000, Gelucire 44/14, Vitamin E TPGS	Carbamazepine	Sethia and Squillante, 2002
Capmul MCM C10, Gelucire 44/14	Ceftriaxone	Cho and Lee et al., 2004
PEG 6000, Myrj 52, Eudragit E100, Carbohydrates (lactose, sorbitol, mannitol, dextrin)	Indomethacin	Valizadeh and Nokhodchi et al., 2004

Table IV. *Examples of stabilization strategies to prevent crystallization of amorphous solid dispersions*

Drugs	Used excipient	Stabilization strategies and results	References
Acetaminophen	PVP, PAA	• Better stabilizing effect of PAA than PVP • Strong molecular interaction with acetaminophen	Miyazaki. et al., 2004
Celecoxib	PVP	• An apparent plateau phase in relaxation enthalpy studies above the 20% of PVP content	Gupta et al., 2004
Etoricoxib	Gelucire 50/13	• Stabilization effect along with biopharmaceutical performance improvement at a low excipient/drug ratio	Shimpi et al., 2005
Felodipine	PVP, HPMC, HPMCAS	• Similar stabilization abilities above 25% polymer concentration. • Strong relation between the moisture absorption tendency and the stabilization effects.	Konno et al., 2008
Indomethacin	$Mg(OH)_2/SiO_2$	• Immobilization of the indomethacin molecules due to mechanochemical reaction between $Mg(OH)_2$ and SiO_2	Watanabe et al., 2002
	PVP, PAA	• Formation of hydrogen bond with indomethacin • Preventing the formation of carboxylic acid dimers	Matsumoto et al., 1999
	Eudragit EPO	• Stabilization effect due to molecular interaction	Chokshi et al., 2008
Ketoconazole	PVP	• Stabilization effect due to anti-plasticizing effect of polymer • Increase in the viscosity of the system and decrease in the diffusion of drug molecules necessary to form a lattice	Van den Mooter et al., 2001
MK-0591	PVP	• Ion–dipole interaction between COO^-Na^+ group of the drug and the cyclic amide group of PVP	Khougaz et al., 2000
Nilvadipine	cl-PVP/MC	• Stabilization effect due to nilvadipine /cl-PVP/MC ternary solid dispersion system	Hirasawa et al., 2003
Nimodipine	PEG/PVP	• Better stabilization effect of nimodipine/PVP K17/PEG 2000 ternary solid dispersion system than nimodipine/PEG 2000 binary system	Urbanetz, 2006
UC-781	PVP	• Stabilization effect due to elevation of T_g of the drug and/or the molecular interaction between the drug and the carrier	Damian et al., 2002

PVP, Poly(vinylpyrrolidone) ; PAA, Poly(vinylpyrrolidone-co-vinylacetate) ; HPMC, hydroxypropylmethylcellulose ; HPMCAS, hydroxypropylmethylcelluloseacetatesuccinate ; cl-PVP, crospovidone ; MC, methylcellulose

forms with different HLB values. Gelucires of low HLB value are used for slow dissolution rates of drugs, whereas high HLB value gelucires are used to improve dissolution of drugs. Labrasol has self-emulsifying effect and is used as a surfactant. Eudragit, on the other hand, is an acrylic polymers used in solid oral dosage forms. Eudragits are either soluble or insoluble in gastro-intestinal fluids.

Other strategies include direct capsule filling and electrostatic spinning technique (Dhirendra and Lewis et al., 2009). In the direct capsule filling technique, the mixture of drug and carrier is filled directly in hard gelatin capsules. As a result, the solid dispersion is manufactured and prevented from changing

into the crystalline state and scaled up for commercial market. But PEGs as carrier are not suitable in this technique because using these carrier results in drug-rich solid layer on surface of solid dispersions (Serajuddin and Sheen et al., 1988). On the other hand, in electrostatic spinning technique, fibers of submicron diameter are formed, which could be used to develop dosage form by direct incorporation of solid dispersions into the capsules (Verreck and Chun et al., 2003).

Above all, overcoming physical instability of solid dispersions is the most difficult task. Physical instability also brings about reduction in dissolution rate and bioavailability. The main cause of physical instability is crystallization of amorphous solid dispersions during storage (Chiou, 1977). The amorphous phase may be converted to thermodynamically stable crystalline phase. To make up for this stability problem, solid dispersion which inhibits the crystallization of amorphous drug, by choosing the polymer (Desai, 2006; Konno and Taylor, 2006; Tanaka and Imai et al., 2006; Verreck and Decorte et al., 2006) that can make certain cross-links or make hydrogen bonding with the drug (Rodier and Lochard et al., 2005; Tanaka and Imai et al., 2005; Konno and Taylor, 2006) so that its nucleation rate can be reduced, is being actively studied (Chiou and Riegelman, 1971; Damian and Blaton et al., 2000; Karatas and Yuksel et al., 2005; Tanaka and Imai et al., 2006). There have been many attempts to overcome this problem which are outlined in Table IV.

Conclusions

As poorly water-soluble compounds become more prevalent in the pharmaceutical markets, there are increased attempts for enhancing oral bioavailability of these drug candidates. Solid dispersions are one of the most promising strategies to solve this problem. Since Sekiguchi and Obi reported solid dispersions for the first time in 1961, they have evolved through generations. Lately, new forms of solid dispersions have developed. These formulations with surface active property reveal improved drug dissolution rate and absorption more than ever. Although some instability issues remain to be solved, continuous attempts are being made to find solutions for these problems. Possibly, with further advancement in material science and deeper understanding of bio pharmaceutics, solid dispersions will become applicable as an essential technique to overcome the predominant problems with poorly water-soluble drugs. Most of the promising new chemical entities are poorly water soluble drugs with insufficient therapeutic effects because of their low bioavailability. The third generation of solid dispersions can improve drug stability and performance by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity. Moreover, new, optimized manufacturing techniques that are easily scalable are also coming out as a result of academic and industrial research.

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