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총설

고체분산체를 이용한 약물의 생체이용율 향상을 위한 전략

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Solid Dispersion as a Strategy to Improve Drug Bioavailability

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Abstract: Solid dispersion is one of well-established pharmaceutical techniques to improve the dissolution and consequent bioavailability of poorly water soluble drugs. It is defined as a dispersion of drug in an inert carrier matrix. Solid dispersions can be classified into three generations according to the carrier used in the system. First and second generations consist of crystalline and amorphous substances, respectively. Third generation carriers are surfactant, mixture of polymer and surfactants, and mixture of polymers. Solid dispersions can be generallyprepared by melting method and solvent method. While melting method requires high temperature to melt carrier and dissolve drug, solvent method utilizes solvent to dissolve the components. The improvement in dissolution through solid dispersions is attributed to reduction in drug particle size, improvement in wettability, and/or formation of amorphous state. The primary characteristics of solid dispersions, the presenceof drug in amorphous state, could be determined by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and fourier-transformed infrared spectroscopy (FTIR). In spite of the significant improvement in dissolution by solid dispersion technique, some drawbacks have limited the commercial application of solid dispersions. Thus, further studies should be conducted in a direction to improve the congeniality to commercialization.

Keywords: Solid dispersion, Amorphous state, Solubility, Dissolution, Bioavailability

1. Introduction

Drug delivery via oral route is considered one of the most attractive ways of administration due to ease of ingestion, pain avoidance and ultimately high patient compliance [1-3]. Thus, most of drugs have been developed as oral dosage forms. Various factors, which influence oral drug absorption and thereby govern the efficacy of drug therapy, are classified as physicochemical variables, physiological variables and dosage form variables [4]. In particular, solubility and permeability of drug are the most important physicochemical factors. Amidon et al. developed a simplified macroscopic approach to *in vivo* drug absorption based on the good correlation between the extent of drug absorption and those factors (solubility and permeability), which was named as Biopharmaceutics Classification System (BCS) [5]. BCS classify drugs into four different groups: Class I. High solubility-high permeability drugs, Class II. Low solubility-high permeability drugs, Class III. High solubility-low permeability drugs, and Class IV. Low solubility-low permeability drugs. Absorption of a class II drug can be prominently improved by attention to the formulation [6]. Whereas, for the improvement of class III and IV drugs, which are limited by poor permeability, the most effective approach is to return to the

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Table 1. Example of commercial products using solid dispersion technique

Trade name	Active ingredient	Company	FDA approval	Use
Sporanox®	Itraconazole	Janseen	1996	Antifungal
Intelence®	Etravirine	Tibotec	2008	HIV-Antiviral agent
Prograf®	Tacrolimus	Astellas	1994	Immunosuppressive agent
Crestor®	Rosuvastatin calcium	AstraZeneca	2003	HMG Co-A reductase inhibitor
Gris-PEG®	Griesofulvin	Pendinol	1975	Antifungal
Cesamet®	Nabilone	Valeant	1985	Antiemetic
Solufen®	Ibuprofen	Sanofi-Aventis	-	NSAID

lead optimization phase of discovery and pick another candidate with more appropriate physicochemical properties. Lindenberg et al. classified 89 drugs among 130 orally administered drugs found in the World Health Organization (WHO) model list in 2004 (Fig. 1) [7]. While class I and III drugs occupied 36 and 38%, respectively, drugs classified as class II and IV, poorly soluble drugs, took up no more than 30%. It has been estimated that about 40 to 70 % of all new chemical entities (NCE) including drugs under development programs is hampered owing to the insufficient aqueous solubility [8]. Thus, various formulation strategies have been developed to improve the bioavailability of poorly water soluble drugs. Some strategies improved the dissolution rate of drug by reduction of particle size to even nano-scale through mechanical milling [9,10], fluid energy micronization [11], spray drying [12]. Lipid-based formulations including micro/nanoemulsion [13], self-emulsifying formulation [14], and lipid nanoparticles [15] have been also reportedto enhance the absorption and bioavailability of poorly water soluble drugs.

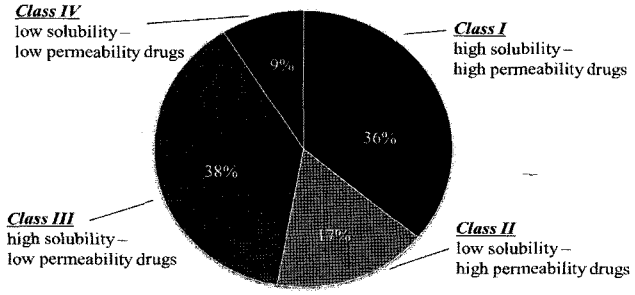

Fig. 1. Biopharmaceutics Classification System of orally administered drugs on the World Health Organizationlist of essential medicines (illustrated based on the results from [7]).

Solid dispersion is one of the most successful strategies to improve the dissolution of poorly water soluble drugs. It was introduced to pharmaceutical industry by Sekiguchi and Obi in 1961 as a formulation approach [16]. Solid dispersion is a dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by melting, or solvent method, according to the definition by Chiou and Riegelman [17]. Corrigan defined solid dispersion as a product formed by converting a fluid drug-carrier combination to the solid state [18].The improved dissolution characteristic of solid dispersion is explained by reduction in the size of drug particles and the consequent increase in surface area [19], improved wettability due to intimate contact with a hydrophilic carrier [20], and forming anamorphous state which doesn't require energy to break up the crystal lattice of the drug during the dissolution process [21].

A vast number of studies regarding solid dispersions including papers and patents have been reported hitherto. Most of the developed formulations showed significant improvement in dissolution and bioavailability [22-24]. However the commercial use of such systems has been limited due to several factors such as preparation method, reproducibility of physicochemical properties, dosage form development, scale up process, and especially physical stability [25]. Accordingly, only a few products have been commercialized on the market (Table 1). Various strategies have been tried recently to overcome the drawbacks and make the preparation practically feasible.

2. Classification of solid dispersions

2.1. First generation

The first application of solid dispersion as a formulation strategy was from Sekiguchi and Obi in 1961 [16]. They proposed eutectic mixture of sulfathiazole, a poorly water soluble drug, with a physiologically inert and easily soluble carrier such as urea. Itwas prepared by melting the compositions followed by a rapid solidification process. Dissolution rate of the drug increased due to the fine dispersion of the drug in solid eutecticmixture and rapid dissolution of soluble matrix. Solid dispersions containing poorly water soluble drugs such as acetaminophen and chloramphenicol were also demonstrated to improve the bioavailability and release rate of drugs by eutectic mixing with urea [26,27]. The next system was developed by Levy and Kanig where drug is molecularly dispersed in carrier in contrast to the eutectic mixture [28, 29]. This dispersion is called a solid solutionwhere drug is dispersed in the carrier on a molecular level. This system showed improved dissolution than eutectic mixture, which was attributed to ultimately reduced particle size [30]. Therefore, further

Table 2. Classification of carriers for solid dispersions

Classification	Examples
First generation carriers - Crystalline compounds	urea, sugars (mannitol), organic acids (succinic acid)
Second generation carriers - Amorphous compounds (polymers)	polyethylene glycol, polyvinylpyrrolidone, polyvinylacetate, polymethacrylate, polymethacrylate, cellulose derivatives (hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylethylcellulose, hydroxypropylmethylcellulose phthalate)
Third generation carriers - Surfactants - Mixture of surfactants and polymers - Mixture of polymers	inulin, polysorbate 80, Compritol® 888 ATO, Gelucire®44/14, mixture of polyethylene glycol and polysorbate 80, mixture of hydroxypropyl methylcellulose and poloxamer 188

researches have been conducted using solid solution approach. Meanwhile, the aforementioned carriers such as urea and mannitol could be classified as first generation carriers which were utilized in solid dispersion for the first time (Table 2). Especially, they were characterized by crystalline properties which were stablethermodynamically but drug release from them was not as prompt as amorphous ones.

2.2. Second generation

Solid dispersions containing amorphous carriers including various hydrophilic polymers (Table 2) could be classified as second generation. This approach resulted in improved dissolution properties over crystalline carriers. Chiou and Riegelman were the first to employ the amorphous substance as a carrier for solid dispersions, using griseofulvin in citric acid [31]. Thereafter, polymers including polyvinylpyrollidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been employed as carriers for solid dispersions [32-35]. Molecularly dispersed drug within amorphous carriers, existing in high energy solid state (i.e., amorphous), doesn't require energy to break up the crystal lattice during dissolution process [21,36]. And the drug is present as supersaturated solution after it has dissolved in the medium. Even though theamorphous solid dispersions could impart highly improved dissolution, they have a disadvantage of thermodynamical instability [37]. The drug in polymeric carrier can crystallize during storage andhas a tendency to nucleate and precipitate from the solution during dissolution process [38]. In this sense, polymer can act as a crystallization inhibitor. However, polymeric carrier has a limitation in stabilizing the supersaturated state of drug. Thus, third generation carriers (Table 2) have been designed to be employed in solid dispersions.

2.3. Third generation

Third generation carriers include surfactants, mixture of polymers and surfactants, and mixture of polymers. It has been reported that drug crystallization could be avoided by using carriers which have surface activity or self-emulsifying properties [39]. Two mechanisms are possible here: promotion of wetting and facilitation of solubilization and absorption [37]. The incorporation of surfactants such as inulin [40], polysorbate 80 [41], Compritol® 888 ATO [42], Gelucire® 44/14 [43-45], and poloxamer [22] have been successful in solid dispersion formulations. In addition, the combination of polymer and surfactant has shown significantly improved dissolution properties in comparison with polymer alone as a carrier. The addition of surfactants such as sodiumdodecyl sulfate, sodium dioctyl sulfosuccinate, and polysorbate 60 to ketoprofen-PEG solid dispersions resulted in about 3 to 5 times higher dissolution than the binary solid dispersion [46]. Phosphatidylcholine, a surface active agent, provided an unusual behavior as a carrier. Although it has poor water solubility, incorporation of phosphatidylcholine at low concentration into the nifedipine-polyethylene glycol solid dispersion resulted in markedly enhanced dissolution rate and bioavailability [47]. This might be attributed to the formation of lipid vesicles which retained nifedipine to some degree during dissolution. However, toxicity problem of surfactants should always be considered when using them as carriers for solid dispersions. Combinations of polymers have also been utilized as carriersfor solid dispersions. Hirasawa et al. reported that nilvadipine-crospovidone-methylcellulose ternary solid dispersions showed not only enhanced dissolution of nilvadipine, but clearly improved the physical stability of amorphous form during storage [48].

3. Mechanism of dissolution enhancement

Several potential mechanisms are related to the enhancement of dissolution by solid dispersion. These include (1) reduction in the drug particle, (2) improvement in wettability, and (3) formation of amorphous state. The specific mechanism (s) involved may depend on the solid-state drug form and type of carrier systems.

3.1. Reduction in the drug particle size

It is well known that drug particle size is one of the most

profound parameters which affect to dissolution of drugaccording to the noted Noyes-Whitney equation. Accordingly, particle size reduction techniques such as milling have been applied to improve the solubility of hydrophobic drugs [10]. Solid dispersions could reduce the particle size via dispersing drug molecules among carriers.The consequent increase in surface area provides faster dissolution and enhanced solubility.

3.2. Improvement in wettability

Physical mixture of drug and carrier sometimes showed a certain improvement in solubility and dissolution, which was mainly due to the improved wettability by hydrophilic carriers [22,24]. In solid dispersion systems, where drug is molecularly dispersed in hydrophilic carriers, the efficacy of improving wettability is maximized and consequently the tendency for particle aggregation is inhibited [17,37]. Surface active agents such as cholic acid, bile salts, and lecithin reinforced this property and resulted in much greater improvements [49,50].

3.3. Formation of amorphous state

The formation of amorphous state is the most important mechanism of solid dispersion in improving dissolution. When drug is molecularly dispersed in carrier, drug loses its crystalline structure, changing to amorphous state. It is obvious that the proportion of carrier is important to change crystalline drug into amorphous state. Carrier in low proportion may not be able to disperse the drug in molecular level efficiently [24]. Drug in amorphous state doesn't require energy to break the crystal lattice [36] and results in supersaturated solution when the solid dispersion system is added to an aqueous medium [51]. The improved rate and extent of release are mainly due to this supersaturation. However, the drug in supersaturated solution has a strong tendency to be crystallized [37]. It is well known that polymeric carrier could inhibit the crystallization of amorphous drug [52-56]. Konno et al. have studied to manifest the mechanism of crystallization and prevention thereof by polymeric carriers [38]. They claimed that even though polymers could not prevent the nucleation of drug in amorphous state, they might be able to inhibit crystal growth. The solution remained as supersaturated state at a level where nucleation was no longer spontaneous. It was also found that the ability to prevent crystallization depends on the nature of polymers [38,57]. Fig. 2 shows the dissolution profiles of solid dispersions containing different carriers [57]. The maximum supersaturated concentrations of tacrolimus from three different solid dispersions were almost similar, however, the rate of recrystallization was different depending on carriers used. The results indicated that it is important to select the appropriate carrier to prepare solid dispersions.

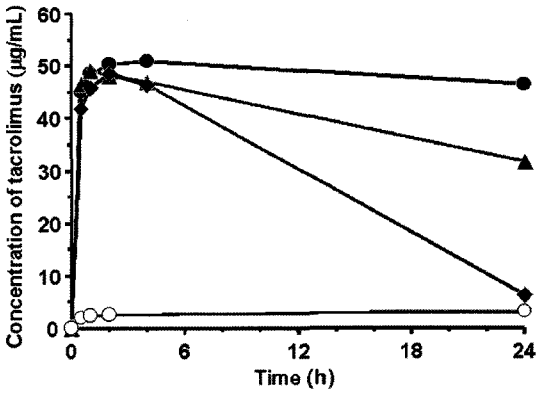

Fig. 2. Dissolution profiles of tacrolimus from solid dispersions. (●) solid dispersion of tacrolimus with HPMC; (▲) solid dispersion of tacrolimus with PVP; (◆) solid dispersion of tacrolimus with PEG 6000; (○) tacrolimus crystalline powder [57].

4. Methods of manufacture

Various preparation methods for solid dispersions have been reported. These methods deal with the challenge of mixing drug and carrier, preferably on a molecular level,while the drug and carrier are generally immiscible [58]. The major processes are melting and solvent methods.

4.1. Melting method

Melting method have been used for the preparation of solid dispersions since Sekiguchi and Obi prepared solid dispersion via simple eutectic mixture [16]. The major advantage of melting method is no use of organic solvent. The basic procedure of melting method is dissolving drug in the molten carrier and the mixture is allowed to cool down to be solidified. Cooling process is of importance since the rate of cooling may affect the solid-state of the drug [59]. A quick cooling process is known to cause higher energy state of drug or smaller crystal size [37]. Sekiguchi et al. facilitated the cooling rate by keeping the sample in an ice bath under agitation until it was solidified [60]. Chiou and Riegelman accelerated the hardening by blowing cold air after spreading it on a stainless steel plate [31]. Various methods including spraying onto a cold surface [28], storing with dry ice [61] and immersion in liquid nitrogen [62] have also been developed. However, the high temperature required to mix drug and carrier properly may be associated with an increased chance of stability problems and material loss during manufacturing due to vaporization or sublimation [63]. Therefore, this method is appropriate especially for the drugs with good thermal stability. Miscibility of drug and carrier is also a prerequisite to prepare solid dispersion via melting method [37]. If there is a miscibility gap in the phase diagram, drug may not be molecularly dispersed in carrier. Moreover, carriers should not have excessively

high viscosity in molten state which may hamper proper mixing [37].

Hot melt extrusion was proposed as an alternative to the conventional melting method. It had been widely used for preparing plastic in the polymer industry. Speiser and Hüttenrach introduced this technique to pharmaceutical field [64,65]. Fig. 3 illustrates a scheme of hot melt extruder. Drug and carrier are mixed and homogenized simultaneously for a shortperiod of time and then shaped as tablets, granules, pellets, sheets, sticks or powder. The processing temperature can be reduced with the use of carbon dioxide as a plasticizer, which extends the area of application to thermolabile drugs [66,67]. Furthermore, this technique offered betterpossibility of commercialization with advantages of continuous production and simplified handling.

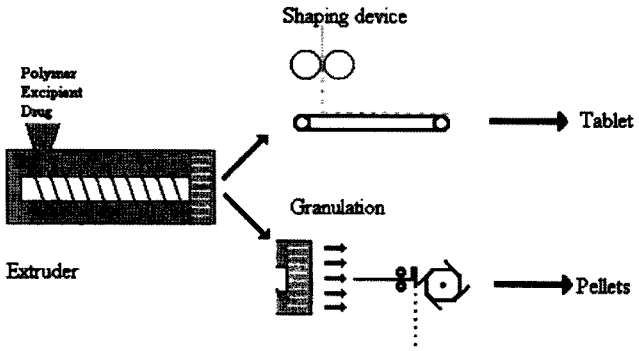

Fig. 3. Scheme of a hot melt extruder [37].

KinetiSol® Dispersing is a novel high energy manufacturing process that has been recently applied to the preparation of solid dispersions. It has already been used in other fields [68]. In this process, drug and carrier areprocessed within a closed fixed volume chamber containing blades rotating at high speed.It allows ultimately reduced exposure time of under 15 s at high temperature compared to over 300 s of hot melt extrusion. Since thermal stress is minimized in this process, thermolabiledrugs and carriers could be employed. It also offers enhanced mixing and increased production output without the aid of a plastisizer. Sincethis technique is not yet firmly established within the pharmaceutical manufacturing, continued researches on this technology are required.

4.2. Solvent method

Because of the limitations of melting method, solvent method has been proposed for an alternative preparation process of solid dispersions. Tachibana and Nakamura were the first to apply solvent method to the preparation of solid dispersions [69]. They dissolved both drug and carrier in organic solvent followed by evaporating the solvent under vacuum to prepare solid dispersions. Solvent evaporation method utilizes volatile solvents such as ethanol, methanol, dichloromethane, and mixtures thereof to dissolve the drug and carrier instead of heating. The solvent is then allowed to evaporate by various processes including vacuum drying [70,71], heating on a hot plate [72], using rotary evaporator [73], a steam of nitrogen [74], spray drying [75,76], freeze drying [40], and using supercritical fluids [77]. Freeze drying involves theadvantages of minimal thermal stress during the drying process and minimized risk of phase separation [78]. However, the low freezing temperature of most organic solvents is a potential problem for the application of freeze drying to prepare solid dispersions (Table 3). Spray drying is one of the attractive drying processes since the solid dispersions prepared by this process possess very fine particle size,and the process time is short due to rapid evaporation of solvent resulting from large specific surface area of droplets. Jung et al. reported that the diameter of solid dispersion particles prepared by spray drying was in the range of 1-10 μm. Besides, the residual amount of organic solvent remaining in the solid dispersions was far below the acceptable limit which is defined in USP [76]. However, it was reported that sometimes drugs may crystallize during the process [79]. An even more fascinating drying process is spray freeze drying [80]. The solvent dissolving drug and carrier is sprayed into cold dry air or liquid nitrogen. The highly porous particles of solid dispersions are obtained by subsequent lyophilization of frozen droplets. This technique could avoid heat and air induced degradation or phase separation of drug and carrier during freezing and drying process.

Table 3. Overview of some organic solvents widely used in preparation of solid dispersions

Solvent	Melting point (℃)	Boiling point (℃)
Water	0	100
Methanol	-93.9	65
Ethanol	-117	78.5
Dichloromethane	-96.7	39.6
Chloroform	-63	62
1-propanol	-85.8	97.4
2-propanol	-127	82.4
Dimethylsulfoxide	19	189
2-methyl-2-propanol (TBA)	25	82

Some of limitations of melting method can beovercome by solvent evaporation method. It becomes possible to use thermolabile drugs to prepare solid dispersion. Likewise, high melting point carriers such as PVP and sugars can be considered as carrier candidates. However, high cost and difficulty in removing solvent completely are the disadvantages associated with solvent evaporation method. The residual solventmay cause significant problems due to its toxicity. Some solvents such as chloroform and dichloromethane, which have been widely used in the preparation of solid dispersions, belong to Class I, the most toxic solvent, according to the ICH

guideline [78]. Evaporating these solvent below the detection limits is almost impractical.

Some modifications on solvent evaporation method have been tried as an effort to minimize the use of organic solvents. Yamashita established solvent wetting method [57]. The selection of organic solvent which can dissolve both drug and carrier is quite limited, and the solvents satisfying this qualification are usually highly toxic. Thus, they selected the solvent which could dissolve drug only. When the solution containing both dissolved drug and suspending carrier allowed to dry, amorphous form of drug was attached to thesurface of dispersed carrier particles. Improvement in dissolution and bioavailability from the solid dispersion prepared by this method was comparable to that bysolvent evaporation method. Park et al. developed a novel concept of solvent method called surface attached method [81,82]. Unlike other solvent methods, they prepared solid dispersions without using any organic solvent. While hydrophilic carrier i.e., hydroxypropyl-β-cyclodextrin was dissolved in water, drug was just dispersed therein. After drying, the dissolved carrier was attached to the surface of dispersed drug particles, which did not change the crystalline form of drug but change the drug from being hydrophobic to hydrophilic. The resultant solid dispersions showed improvement in solubility and dissolution. Modified methods, aforementioned, have strong advantages over solvent evaporation method on an industrial scale. They require less or no need to remove organic solvents and have reduced toxicity [81,83]. Moreover, surface attached method may not have physical stability problems since the drug particles exist as crystalline form. While Joe et al. reported that the efficacy of improvement is in the order of solvent evaporation method > solvent wetting method > surface attached method [83].

5. Characterization of solid dispersions

The most important characteristic of solid dispersions is the presence of drug in amorphous state. Several techniques are available to differentiate between amorphous and crystalline materials. Differential scanning calorimetry (DSC) is the most frequently used technique to characterize solid dispersions. In DSC, sample and reference are heated simultaneously with a constant heating rate, and the amount of energy required for keeping the temperature of the two identical is measured [84]. Thermal events such as glass transition temperature (T_g) and melting point can be observed in the thermogram. Since amorphous material do not show a sharp phase change from solid to liquid at a definite temperature, the distinction of amorphous from crystalline state could be determined from the present of melting point. As this technique is also a way of quantitative analysis, the degree of crystallinity can also be calculated. However, it has been reported that DSC cannot detect the crystallinity under 2% [85]. T_g is also an important parameter which can be measured by DSC. Since it indicates a borderline between high and low molecular mobility, it is known to be related to the stability of amorphous solid dispersions [86].

Powder X-ray diffraction (PXRD) is a technique for structural characterization of materials [87]. When X-ray is irradiated to powder sample, the sample produces constructive interference and the diffracted X-ray is then detected. The result is present as a diffractogram by recording the intensity of diffracted X-rays according to their respective angles. While a crystallinepattern consists of a series of sharp peaks, amorphous materials show a broad background signal. When the crystalline drug is formulated to solid dispersions, the series of sharp peaks will not be observed.

Fourier-transformed infrared spectroscopy (FTIR) also can be used for thedetermination of crystallinity. The ratio of the heights of two peaks attributed to the crystalline and the amorphous phases gives information about the degree of crystallinityof the sample [88]. In addition, water vapor sorption, isothermal microcalorimetry, dissolution calorimetry measurement, and dynamic mechanical analysis are available to detect the crystallinity in solid dispersions [78].

6. Limitations of solid dispersions

Even though the solid dispersion techniqueis an innovative method to improve the bioavailability of poorly water soluble drugs, the following factors have limited the commercial application of solid dispersions; preparation method, reproducibility of physicochemical properties, formulation development, scale up process and physical stability.

Melting method is not appropriate to thermolabile drugs and carriers having high melting points. Besides, high cost may be incurred as high energy is prerequisite to increase the temperature. And the process including heating, solidification by cooling, and millingis quite complex and difficult. In case of solvent evaporation method, it is sometimes difficult to find proper solvents which can dissolve both drug and carrier. And the required volume of solvent is rather large, which may bring about high cost and environmental issues. Moreover, solvent removal is typically expensive, time consuming, and often time incomplete. Especially, the residual solvent left in solid dispersion systems may cause critical toxicology problems *in vivo*.

Furthermore, it is difficult to reproduce the physicochemical properties of solid dispersions due to its high sensitivity to the process parameters such as heating rate and temperature, holding time at high temperature, cooling rate and conditions,

and evaporation rate. Especially, the physicochemical properties of solid dispersions can be altered as the scale of process is changed, since heating and cooling rates, or evaporation rate under large scale may differ greatly from that from a smaller scale.

The required amount of carrier is a potential problem of solid dispersionsduring formulation development. Relatively large amount of carrier is essential to form amorphous solid dispersions and physically stabilize the systems. Several studies have been reported that insufficient amount of carrier resulted in some degree of drug crystallinity in solid dispersions [24]. However, using such high amount of carrier is expensive and it may cause difficulty in product design. The large size of developed dosage form may reduce the patient compliance. Therefore, it is important to optimize the ratio of drug and carrier in formulation and minimize the amount of carrier used.

Physical stability is the most concerning drawback of solid dispersions. Since amorphous state is less stable than the crystalline state, it tends to change from amorphous (higher energy) state to crystalline (lower energy) state, and consequently drug may recrystallize from solid dispersions during the manufacturing process or under storage conditions. Drug could be recrystallized from the solid dispersion during the manufacturing process when it is dissolved beyond the solubility in a carrier [89]. Stress factors such as temperature and humidity may accelerate drug recrystallization under storage conditions and it may lead to an unfavorable change in dissolution profile [63].

7. Recent and future strategies to overcome the drawbacks

Solid dispersion techniques have been advanced in a direction to improve the feasibility of commercialization. The limitations related to manufacturing have been gradually resolved by the emergence of advanced techniques such as spray drying, hot melt extrusion, and KinetiSol® Dispersing. Spray drying technique could reduce the amount of residual solvent below the acceptable level. Hot melt extrusion and KinetiSol® Dispersing techniques have shown their suitability for scale up with advantages of continuous production and simplified handling. Moreover, drug candidates associated with melting method have been extended to thermolabile drugs.

While solvent wetting and surface attached methods bypassed the limitationsof solvent method through modifying the concept, it is well known that the solvent should dissolve both drug and carrier in order to improve the dissolution significantly. However, instead of pursuing further improvementsin dissolution by dissolving all components, these methods could avoid the concern about residual solvents and subsequent toxicity problems by reduction or avoidance of toxic solvents. It was reported that in a certain cases, the extent of improvement through solvent wetting method was comparable to solvent evaporation method [57].

Recently many studies have been conducted to overcome the physical stability problems of solid dispersions. Interaction between drug and carrier, such as ion-dipole interaction and intermolecular hydrogen bonding, is one of the strategiesto improve the physical stability of solid dispersions. Tayler and Zografi demonstrated that the hydrogen bond formed between the amide carbonyl group of PVP and the hydroxyl group of indomethacin could improve the stability of solid dispersions even in an elevated temperature [36,90]. Nepal et al. reinforced the stability of Coenzyme Q_{10} solid dispersions by incorporating Aerosil® 200 as an adsorbent into the system [24]. Large surface area of Aerosil® 200 provided site for drug adsorption and limit recrystallization process and the hydrogen bond between the drug and silanol group of Aerosil® 200 prevented recrystallization process.

One of the major focuses in future researches should be the extension of carrier candidates for solid dispersions. The number of carriers which are available for oral use have been restricted hitherto. Some carriers such as surface active agents and self-emulsifying agents used in non-oral applications could be revealed to be useful for oral use afterappropriate toxicological tests. It is important to note that the improvements from solid dispersions depend on the nature of carriers and formulations thereof. Thus the success of dosage form developments could be increased through an extensive screening of carriers.

8. Conclusions

40 years has been passed since solid dispersion technique was first introduced to pharmaceutical industry by Sekiguchi and Obi in 1961. Solid dispersions have shown a great potential for improving the bioavailability of poorly water soluble drugs. Most of the promising new chemical entitiesare having problems with the low solubility, and solid dispersions is under the spotlight with the expectationof significant improvement in bioavailability of poorly water soluble drugs. However some factors still limit the commercializationof solid dispersions. Accordingly, further intensive studies should be conducted to resolve the remaining drawbacks.

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