

Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs

ABU T. M. SERAJUDDIN[†]

Contribution from *Pharmaceutics R & D Department, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, New Jersey 08903-0191.*

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Abstract □ Although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily because of manufacturing difficulties and stability problems. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures. They were then pulverized, sieved, mixed with relatively large amounts of excipients, and encapsulated into hard gelatin capsules or compressed into tablets. These operations were difficult to scale up for the manufacture of dosage forms. The situation has, however, been changing in recent years because of the availability of surface-active and self-emulsifying carriers and the development of technologies to encapsulate solid dispersions directly into hard gelatin capsules as melts. Solid plugs are formed inside the capsules when the melts are cooled to room temperature. Because of surface activity of carriers used, complete dissolution of drug from such solid dispersions can be obtained without the need for pulverization, sieving, mixing with excipients, etc. Equipment is available for large-scale manufacturing of such capsules. Some practical limitations of dosage form development might be the inadequate solubility of drugs in carriers and the instability of drugs and carriers at elevated temperatures necessary to manufacture capsules.

Introduction

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs,¹ there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage

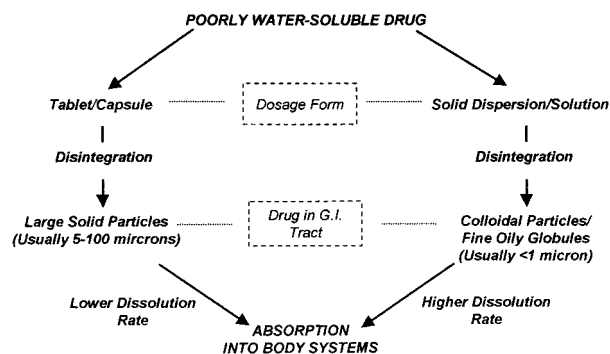


Figure 1—A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

form may also be problematic because of handling difficulties and poor wettability.

In 1961, Sekiguchi and Obi² developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome. This method, which was later termed solid dispersion,³ involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi² suggested that the drug was present in a eutectic mixture in a microcrystalline state. Later, Goldberg et al.^{4,5} demonstrated that all the drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

The advantage of solid dispersion, compared with conventional capsule and tablet formulations, is shown schematically in Figure 1.⁶ From conventional capsules and tablets, the dissolution rate is limited by the size of the primary particles formed after the disintegration of dosage forms. In this case, an average particle size of 5 μm is usually the lower limit, although higher particle sizes are preferred for ease of handling, formulation, and manufacturing. On the other hand, if a solid dispersion or a solid solution is used, a portion of the drug dissolves immediately to saturate the gastrointestinal fluid, and the excess drug precipitates out as fine colloidal particles or oily globules of submicron size.

Because of such early promises in the bioavailability enhancement of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical field. Numerous papers on various aspects

[†] Present address: Novartis, 59 Route 10, Building 401, East Hanover, New Jersey 07936.

of solid dispersion were published since 1961; Chiou and Riegelman³ and Ford⁷ reviewed the early research in this area. Despite an active research interest, the commercial application of solid dispersion in dosage form design has been very limited. Only two products, a griseofulvin-in-poly(ethylene glycol) solid dispersion (Gris-PEG, Novartis) and a nabilone-in-povidone solid dispersion (Cesamet, Lilly) were marketed during three decades following the initial work of Sekiguchi and Obi in 1961. The objectives of the present article are to critically review some of the limitations of solid dispersion that prevented its wider commercial application and to discuss how the situation is now changing because of the availability of new types of vehicles and the development of new manufacturing technologies.

Limitations of Solid Dispersion Systems

Problems limiting the commercial application of solid dispersion involve (a) its method of preparation, (b) reproducibility of its physicochemical properties, (c) its formulation into dosage forms, (d) the scale up of manufacturing processes, and (e) the physical and chemical stability of drug and vehicle. Some of the issues are discussed next.

Method of Preparation—In their pioneering study, Sekiguchi and Obi² prepared solid dispersions of sulfathiazole in such carriers as ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide, and urea by melting various drug-carrier mixtures. To minimize melting temperatures, eutectic mixtures of the drug with carriers were used. Yet, in all cases, except acetamide, the melting temperatures were $>110^{\circ}\text{C}$, which could chemically decompose drugs and carriers.³ High temperatures ($>100^{\circ}\text{C}$) were also utilized by Goldberg et al. in preparing acetaminophen-urea,⁴ griseofulvin-succinic acid,⁴ and chloramphenicol-urea⁸ solid dispersions. After melting, the next difficult step in the preparation of solid dispersions was the hardening of melts so that they could be pulverized for subsequent formulation into powder-filled capsules or compressed tablets. Sekiguchi and Obi² cooled the sulfathiazole-urea melt rapidly in an ice bath with vigorous stirring until it solidified. Chiou and Riegelman⁹ facilitated hardening of the griseofulvin-PEG 6000 solid dispersion by blowing cold air after spreading it on a stainless steel plate and then storing the material in a desiccator for several days. In preparing primidone-citric acid solid dispersions, Summers and Enever¹⁰ spread the melt on Petri dishes, cooled it by storing the Petri dishes in a desiccator, and finally placed the desiccator at 60°C for several days. Allen et al.¹¹ prepared solid dispersions of corticosteroids in galactose, dextrose, and sucrose at 169, 185, and 200°C , respectively, and then placed them on aluminum boats over dry ice. Timko and Lordi¹² also used blocks of dry ice to cool and solidify phenobarbital-citric acid mixtures that had previously been melted on a frying pan at 170°C . The fusion method of preparing solid dispersion remained essentially similar over the period of time. More recently, Lin and Cham¹³ prepared nifedipine-PEG 6000 solid dispersions by blending physical mixtures of the drug and the carrier in a V-shaped blender and then heating the mixtures on a hot plate at $80\text{--}85^{\circ}\text{C}$ until they were completely melted. The melts were rapidly cooled by immersion in a freezing mixture of ice and sodium chloride, and the solids were stored for 24 h in a desiccator over silica gel before pulverization and sieving. Mura et al.¹⁴ solidified naproxen-PEG melts in an ice bath and the solids were then stored under reduced pressure in a desiccator for 48 h before they were ground into powders with a mortar and pestle. In another study, Owusu-Ababio et al.¹⁵ prepared a mefenamic acid-PEG solid dispersion by heating the drug-carrier mixture on a hot plate to a temperature above

the melting point of mefenamic acid (253°C) and then cooling the melt to room temperature under a controlled environment.

Another commonly used method of preparing a solid dispersion is the dissolution of drug and carrier in a common organic solvent, followed by the removal of solvent by evaporation.^{9,16,17} Because the drug used for solid dispersion is usually hydrophobic and the carrier is hydrophilic, it is often difficult to identify a common solvent to dissolve both components. Large volumes of solvents as well as heating may be necessary to enable complete dissolution of both components. Chiou and Riegelman⁹ used 500 mL of ethanol to dissolve 0.5 g of griseofulvin and 4.5 g of PEG 6000. Although in most other reported studies the volumes of solvents necessary to prepare solid dispersions were not specified, it is possible that they were similarly large. To minimize the volume of organic solvent necessary, Usui et al.¹⁸ dissolved a basic drug in a hydroalcoholic mixture of 1 N HCl and methanol, with drug-to-cosolvent ratios ranging from 1:48 to 1:20, because as a protonated species, the drug was more soluble in the acidic cosolvent system than in methanol alone. Some other investigators dissolved only the drug in the organic solvent, and the solutions were then added to the melted carriers. Vera et al.¹⁹ dissolved 1 g of oxodipine per 150 mL of ethanol before mixing the solution with melted PEG 6000. In the preparation of piroxicam-PEG 4000 solid dispersion, Fernandez et al.²⁰ dissolved the drug in chloroform and then mixed the solution with the melt of PEG 4000 at 70°C . Many different methods were used for the removal of organic solvents from solid dispersions. Simonelli et al.¹⁶ evaporated ethanolic solvent on a steam bath and the residual solvent was then removed by applying reduced pressure. Chiou and Riegelman⁹ dried an ethanolic solution of griseofulvin and PEG 6000 in an oil bath at 115°C until there was no evolution of ethanol bubbles. The viscous mass was then allowed to solidify by cooling in a stream of cold air. Other investigators used such techniques as vacuum-drying,^{20,21} spray-drying,²²⁻²⁵ spraying on sugarbeads using a fluidized bed-coating system,²⁶ lyophilization,²⁷ etc., for the removal of organic solvents from solid dispersions. None of the reports, however, addressed how much residual solvents were present in solid dispersions when different solvents, carriers, or drying techniques were used.

Reproducibility of Physicochemical Properties—In their pioneering studies, Sekiguchi and Obi² observed that manufacturing conditions might greatly influence the physicochemical properties of solid dispersions formed. They cooled drug-carrier melts under vigorous stirring conditions to obtain fine and uniform drug particles in solid dispersions. Various investigators observed that heating rate, maximum temperature used, holding time at a high temperature, cooling method and rate, method of pulverization, and particle size may greatly influence the properties of solid dispersions prepared by the melt method. McGinity et al.²⁸ prepared solid dispersions of tolbutamide in urea and PEG 6000 by flash cooling in a bath of dry ice and acetone or by gradual cooling over a period of several hours by immersion in an oil bath. The powder X-ray diffraction patterns of the tolbutamide-urea solid dispersion differed markedly depending on the cooling rate. The slow-cooled solid dispersion of tolbutamide in urea demonstrated a complete lack of crystallinity for both the drug and urea, whereas the flash-cooled dispersions showed only the absence of drug crystallinity. In the powder X-ray diffraction patterns of tolbutamide-PEG 6000 solid dispersions, peaks for both tolbutamide and PEG 6000 were observed; however, their degree of crystallinity in flash-cooled samples was less than that in the slow-cooled

samples. In another study, a metastable amorphous form of nifedipine was formed in its solid dispersions in PEG 4000 and PEG 6000 when the drug-carrier melts were cooled rapidly, whereas slow cooling of melts or powdering of solidified mass resulted in the crystallization of drug.²⁹ Ginés et al.³⁰ studied the effect of fusion temperature on oxazepam-PEG 4000 solid dispersions. Microscopic examination revealed the presence of crystalline oxazepam and the spherulitic form of PEG 4000 in solid dispersions prepared by fusion at 100 °C. In contrast, a fusion temperature of 150 °C produced a solid dispersion with no crystalline form of the drug and the presence of PEG 4000 in a hedritic form. Complete dissolution of drug in the carrier at 150 °C in contrast to 100 °C was reported to be responsible for such a difference in physicochemical properties of the solid dispersions produced. Dordunoo et al.³¹ also observed a change of triamterene and temazepam from crystalline to amorphous form in poly(ethylene glycol) solid dispersions when the fusion temperature was increased from 100 to 150 °C. Such changes in physical states of drugs in solid dispersions result into differences in drug dissolution rates in aqueous media.³⁰ Drug-to-carrier ratio and particle size of solid dispersions were also reported to influence the dissolution rate of drug.³²

The properties of solid dispersions prepared by the solvent method may also vary depending on manufacturing conditions. The solvent method usually leads to amorphous forms of drugs. However, some crystallinity of drug may be observed depending on the drug-to-carrier ratio used.³³ Although no detailed studies were reported in the literature, it is expected that the nature of solvent used, drug-to-solvent and carrier-to-solvent ratios, drying method, and drying rate may significantly influence the physicochemical properties of solid dispersions formed.

Dosage Form Development—Solid dispersion must be developed into convenient dosage forms, such as capsules and tablets, for their clinical use and successful commercialization. As already mentioned, solid dispersions produced by the melt method are usually hardened at very low temperatures and then pulverized with mortars and pestles. Similarly, solid dispersions produced by the solvent method are also pulverized after solvent removal and hardening. Some of the challenges in the dosage form development of such materials are difficulty of pulverization and sifting of the dispersions, which are usually soft and tacky, poor flow and mixing properties of powders thus prepared, poor compressibility, drug-carrier incompatibility, and poor stability of dosage forms. However, there are very few reports in the literature addressing these important issues.⁷ Even the limited number of reports describing any dosage form developmental aspects of solid dispersions only confirm that the task of formulating solid dispersions into capsules or tablets may be a very complex and difficult one. In developing a tablet formulation for the indomethacin-PEG 6000 solid dispersion, Ford and Rubinstein³⁴ reported that the solid dispersion was not amenable to wet granulation because water could disrupt its physical structure. In addition, the dispersion was soft and tacky. To overcome these problems, the authors adopted an *in situ* dry granulation method where the excipients (calcium hydrogen phosphate and sodium starch glycolate) were preheated and rotated in a water-jacketed blender at 70 °C, and the indomethacin-PEG 6000 mixture that melted at 100 °C was then added to the moving powder. After mixing, the granules were passed through a 20-mesh sieve and allowed to harden at 25 °C for 12 h. Then, the granules were mixed with a relatively high concentration of magnesium stearate (1%) and compressed into tablets. To process 100 mg of solid dispersion, 506 mg of other excipients were used, thus making the final weight

of a 25-mg indomethacin tablet 606 mg. Yet, the tablet did not disintegrate in water despite the use of a large amount of excipients. It dissolved slowly by erosion, and the dissolution rate decreased on aging of the tablet. In another study, the same investigators used an essentially similar *in situ* dry granulation method for the preparation of tablet dosage forms for a chlorpropamide-urea solid dispersion, where the drug, the carrier, and the excipients were mixed in a rotating flask on a water bath maintained at 100 °C.³⁵ The properties of these formulations also changed with time, and the authors concluded that aging could "limit their usefulness as prospective dosage forms". During the development of a tablet formulation for a furosemide-poly(vinylpyrrolidone) (PVP) solid dispersion, Akbuga et al.³⁶ observed that method of preparation, choice of disintegrant and particle size of solid dispersions were critical factors in determining the properties of tablets produced. Despite the use of relatively large amounts of disintegrants, the tablets did not disintegrate. Rather, they dissolved by erosion only, and the erosion rate varied depending on the disintegrant used. In addition, the dissolution rate of tablets prepared by double compression (slugging and recompression of dry granules) was much slower than that of the tablets prepared by single compression. The dissolution rate of tablet was also dependent on the particle size of solid dispersion used; the rate decreased by a factor of 5 when 100-mesh particles were used in place of 80-mesh particles. Also, the compressibility of solid dispersion decreased with a decrease in particle size. In another study, Sjökvist and Nystrom³⁷ overcame the compression difficulties due to sticking of griseofulvin-xylitol solid dispersions to dies and punches by lubricating die wall and punch faces with 1% (w/w) magnesium stearate suspension before the compression of each tablet. The authors observed that the dissolution rate of tablet was highly sensitive to compression pressure. The sticking of solid dispersion to dies and punches might become so problematic that Kaur et al.³⁸ resorted to placing small pieces of grease-proof paper between metal surfaces and granules before the compression of tablets.

The lack of disintegration and the slow dissolution of tablets prepared from solid dispersions could be related to the soft and waxy nature of carriers used (e.g., PEG) in many of the reported studies. Such carriers essentially act as strong binders within tablets. During compression, the carriers could plasticize, soften, or melt, filling the pores within tablets and thus making them nondisintegrating. It is also possible that the softened and melted carriers coat the disintegrants and other ingredients used in tablets, and such a coating, along with the reduction of porosity of tablets, make the disintegrants ineffective. Use of a very high ratio of solid dispersion to added excipient might alleviate the problem. In one study,¹⁵ 270 mg of microcrystalline cellulose (Avicel) was used to formulate 30 mg of mefenamic acid-PEG solid dispersion into a tablet with good dissolution. The use of such a high ratio of added excipient would, however, greatly increase the size of tablet and might, therefore, be impractical in most formulations.

Scale Up of Manufacturing Processes—Because very few solid dispersion products prepared by melt or solvent methods have been marketed, there are practically no reports on the scale up of such products. It is apparent from the discussion just presented that the scale up of the methods of preparation of solid dispersions and their dosage forms could be very challenging. In most of the studies reported in the literature, solid dispersions by the melt method were prepared in a small scale by heating drug-carrier mixtures in beakers, frying pans, etc. that were placed on hot plates and then cooling the melts in an ice bath, a dry ice-acetone mixture, etc.^{2-5,7-14} Because there could be condensation of moisture over solid disper-

sions during cooling to low temperatures, strict protection from moisture was necessary in all cases. The scale up challenges may be illustrated with the example of the preparation of a phenytoin-PEG 4000 solid dispersion by Yakou et al.³⁹ The drug-carrier mixture was heated at 250 °C under constant stirring until a clear homogeneous melt was obtained, and the melt was air-cooled by spreading on stainless steel trays. The trays were stored in a desiccator for 3 days to enhance solidification of the solid dispersion. The resulting material was then crushed in a cutter mill, and the powders were sieved to collect a sieve fraction of 105–177- μ m particle size for use in the dosage form. The scale up of such a method would be difficult and it might even be impractical in many cases because of possible degradation of both drug and carrier at high temperatures used. The scale up might also necessitate a large capital investment because a chemical plant-like facility, rather than a common pharmaceutical dosage form manufacturing plant, would be required to process and manufacture the products. For scale up of the cooling process, Lefebvre et al.⁴⁰ recommended such continuous operation as cooling on the surfaces of moving belts or rotating cylinders, and spray congealing. The practical application of the methods, however, was not demonstrated. Kennedy and Niebergall⁴¹ described a hot-melt fluid bed method whereby nonpareils could be coated with PEGs having molecular weights between 1450 and 4600. A similar method can possibly be used to deposit solid dispersions on nonpareils and might in the future find application in the manufacture and scale up of solid dispersion formulations.

The physicochemical properties and stability of solid dispersions may also be affected by scale up because heating and cooling rates of solid dispersions under large-scale manufacturing conditions may differ greatly from that in small beakers.^{28,29} Drug-carrier compatibility at a high temperature also requires careful consideration. Dubois and Ford⁴² reported the chain scission of PEG 600 during fusion with disulfiram, furosemide, chlorthiazide, and chlorpropamide.

The scale up of the solvent method of preparing solid dispersions may also be very challenging. A chemical plant environment would be necessary to evaporate hundreds and even thousands of liters of organic solvents necessary to prepare solid dispersions for kilogram quantities of drugs.^{17,20} The cost of recovery of these solvents may be very high. Removal of residual amounts of potentially toxic organic solvents such as chloroform and methanol from large masses of material may be difficult because the solid dispersions are usually amorphous and may exist in viscous and waxy forms. Solvates may also be formed with drugs and carriers. Because most dosage form manufacturing facilities are not equipped to handle large volumes of organic solvents, one way to resolve the issue might be the designation of solid dispersion as an active pharmaceutical ingredient or bulk drug substance. In that case, the responsibility of the manufacture of solid dispersion can be shifted to the chemical plant. It would be necessary to conduct all developmental activities using the solid dispersion, so this approach might not be suitable for situations where active pharmaceutical ingredients have multiple uses (e.g., oral and parenteral).

The final step in the manufacturing process, which is the conversion of solid dispersions into stable and marketable dosage forms, may be the most difficult one to scale up, optimize, and validate. Most of the commonly used solid dispersion vehicles are soft and sticky and, as a result, the pulverized forms of solid dispersions produced by such vehicles may not be amenable to processing by high-speed capsule or tablet filling machines.

Stability—The physical instability of solid dispersions due to crystallization of drugs was the subject of most published reports in the literature.^{3,7} In a solid dispersion prepared by the melt method, a certain fraction of the drug may remain molecularly dispersed, depending on its solubility in the carrier used, thus forming a solid solution. How the excess drug exists may greatly depend on the method of manufacture of the system; it may, as a whole or in part, form a supersaturated solution, separate out as an amorphous phase, or crystallize out. The supersaturated and amorphous forms may, in turn, crystallize out on aging. Similarly, certain carriers may also exist in thermodynamically unstable states in solid dispersions and undergo changes with time. Chiou⁴³ reported that griseofulvin precipitated out in an amorphous form in a griseofulvin-PEG 6000 solid dispersion during the time of its preparation. The amorphous material crystallized out on aging, except when the drug concentration in the dispersion was 5% or less. Ford and Rubinstein⁴⁴ attributed similar crystallization as the cause for a decrease in dissolution rate of drug from indomethacin-PEG 6000 solid dispersions with time. The decrease in the dissolution rate of indomethacin was also dependent on drug concentration in the solid dispersion. The decrease was greater for a higher drug concentration because a larger fraction of drug crystallized out. In another study, Suzuki and Sunada⁴⁵ observed that on exposure of a nifedipine-nicotinamide-hydroxypropylmethylcellulose (HPMC) solid dispersion to 60% RH at 30 °C or 75% RH at 40 °C for 1 month, nifedipine converted from the amorphous to the crystalline state, thus lowering the dissolution rate of nifedipine drastically. No conversion of nifedipine to the crystalline state was observed when the solid dispersion was stored at an elevated temperature in the absence of humidity. Although the presence of HPMC facilitated the conversion of nifedipine to an amorphous state during the cooling of drug-nicotinamide melt to room temperature at the time of manufacturing, it did not prevent the subsequent crystallization of drug under humid conditions. Pronounced decreases in dissolution rates due to drug crystallization were also reported for tablets prepared from solid dispersions.^{34,35} No such decrease in dissolution rate on aging was observed by Khalil et al.⁴⁶ in corticosteroid-PEG solid dispersions prepared with a drug-to-carrier ratio of 1:99, possibly because most of the drug was molecularly dispersed in the carrier. The corticosteroid, however, exhibited chemical degradation due to oxidation by the peroxides present in PEG. The cooling rate of solid dispersions may also significantly influence their aging behavior. It has been reported that the crystallinity of drug in solid dispersions is less influenced by aging when a slow cooling rate is used because thermodynamically more stable systems are produced during the time of preparation.^{47,48}

The conversion of drug to crystalline state is also the primary stability issue with solid dispersions prepared by the solvent method. PVP, which is commonly used as a carrier in such solid dispersions, is amorphous and does not convert to a crystalline state. However, certain other carriers may convert from their amorphous states to crystalline states in solid dispersions. Zografis and co-workers^{49,50} extensively studied the physicochemical properties of the amorphous states of drugs and excipients and observed that the crystallization of amorphous materials is facilitated by moisture. This effect is why strict protection from moisture is necessary during the preparation and storage of most solid dispersions. Doherty and York⁵¹ studied the stability of furosemide-PVP solid dispersion in the temperature range of 6 to 45 °C and 40% RH for up to 1 year. They did not observe any crystallization of furosemide and suggested that PVP may indeed act as a

stabilizer in the solid dispersion by retarding crystallization of drug at a relatively low humidity. Rapid crystallization of furosemide in the solid dispersion was, however, evident when the humidity was raised to 75% RH. Similar observations were also made by Guillaume et al.⁵² for an oxodipine–PVP solid dispersion where no crystallization of oxodipine was observed in 18 months when samples were stored under 55% RH at various temperatures, but the drug crystallized out at 80% RH. The stabilization of drugs in amorphous forms in solid dispersions is an active area of research in the pharmaceutical field. For an indomethacin–PVP solid dispersion system, Taylor and Zografis⁵³ suggested that hydrogen bonding between the drug and PVP might offer an explanation for the absence of drug crystallization. Lu and Zografis⁵⁴ recently demonstrated that indomethacin forms a completely miscible amorphous mixture with citric acid and PVP when the weight fraction of PVP in the ternary mixture exceeds 0.3 weight fraction. Thus, both the choice of carrier and the drug-to-carrier ratio are important considerations in the stabilization of solid dispersions.

Breakthroughs in Solid Dispersion Technology

Because of the various limitations just mentioned, it is not surprising that the solid dispersion system, despite its many potential advantages, has not been widely used in pharmaceutical dosage forms. Under the present health care economic climate, the goal of any drug development program in the pharmaceutical industry is to rapidly progress a new chemical entity from the discovery stage to clinical testing to determine whether it is safe and clinically effective. The limited supply of the bulk drug substance at the early drug development phase and the accelerated time line would not allow a formulator to address most of the challenges (*vide supra*) of a solid dispersion formulation. Most importantly, if a compound proves promising in early clinical testing, the scale up of complex manufacturing processes for the development of marketable dosage forms cannot be ensured.

Two recent breakthroughs in the formulation of solid dispersion systems involve (1) the development of technologies to fill solid dispersions directly into hard gelatin capsules and (2) the availability of surface-active and self-emulsifying carriers. As a result, there is renewed interest in such systems for use in commercial development of drug products.^{6,55}

Direct Capsule-Filling—Although the filling of semi-solid materials into hard gelatin capsules as melts, which solidify at room temperature, was first described by Francois and Jones in 1978,⁵⁶ it was not until much later that the potential application of the technique for solid dispersions was fully realized. Chatham⁵⁷ reported the possibility of preparing PEG-based solid dispersions by filling drug–PEG melts in hard gelatin capsules. By using PEG with molecular weights ranging from 1000 to 8000, Serajuddin et al.,⁵⁸ however, demonstrated that a PEG by itself might not be a suitable carrier for solid dispersion of poorly water-soluble drugs intended for direct filling into hard gelatin capsules. They dissolved a poorly water-soluble drug, REV5901, in molten PEG 1000, PEG 1450, and PEG 8000 and filled the hot solutions into hard gelatin capsules such that each size 0 capsule contained 100 mg of drug and 550 mg of PEG. At room temperature, solid plugs were formed inside the capsules, where the drug remained molecularly dispersed in the carriers. Although a sink condition existed for the dissolution of 100 mg of the weakly basic REV5901 ($pK_a \sim 3.6$) in 900 mL of simulated gastric fluid (drug solubility = 0.7 mg/mL at 37 °C), the dissolution of drug from all PEG-based solid dispersions was incomplete.

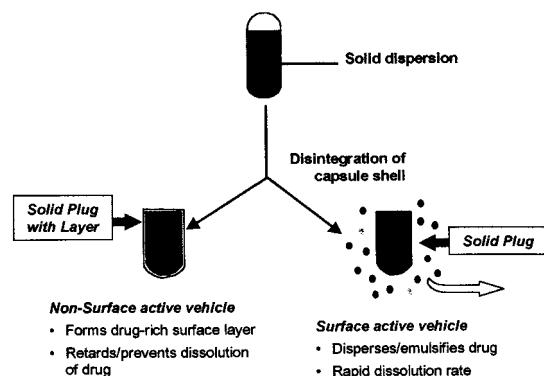


Figure 2—A schematic representation of the comparative dissolution of a poorly water-soluble drug from surface-active versus nonsurface-active vehicles.

Because the water-soluble carrier dissolved more rapidly than the drug, drug-rich layers were formed over the surfaces of dissolving plugs, which prevented further dissolution of drug from solid dispersions. The dissolution was practically zero at $pH > 2$, where the solubility of drug was low and a drug layer coated the surface of the solid plug as soon as the capsule shell disintegrated. Corrigan⁵⁹ also reported the possibility of such a retardation of drug dissolution from solid dispersions.

Surface-Active Carriers—The direct filling of melts into hard gelatin capsules would not be a viable method for the preparation of solid dispersions unless the formation of drug-rich layers on the surfaces of dissolving plugs could be prevented. Serajuddin et al.^{58,60} achieved a complete dissolution of drug from solid dispersions by using surface-active or self-emulsifying carriers. The vehicles acted as dispersing or emulsifying agents for the liberated drug, thus preventing the formation of any water-insoluble surface layers. Although the liberated drug remained undissolved in the dissolution medium when its concentration exceeded its saturation solubility, it was dispersed or emulsified in a finely divided state because of surface activity of the dissolved vehicle.^{58,60} The high surface area of a drug produced in this way would facilitate its dissolution in the gastrointestinal fluid, especially in the presence of bile salts, lecithin, and lipid digestion mixtures.⁶¹

The advantage of a surface-active carrier over a nonsurface-active one in the dissolution of drug from a capsule formulation is shown schematically in Figure 2.⁶ The physical state of drug in a solid dispersion must, however, be carefully considered in evaluating the advantage of a surface-active vehicle. As mentioned earlier, the drug can be molecularly dispersed in the carrier to form a solid solution or it can be dispersed as particulates. It can also be both partially dissolved and partially dispersed in the carrier. The potential for the formation of a continuous drug-rich surface layer is possibly greater if the drug is molecularly dispersed, whereas the drug dispersed as particulates may be more prone to dissociation from the water-soluble matrix. It is, however, rare that the drug is dispersed just as particulates and is not at least partially dissolved in the vehicle. Therefore, a surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs.

The interest in surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs increased greatly in recent years.^{58,60,62–67} For ease of manufacturing, the carriers must be amenable to liquid filling into hard gelatin capsules as melts. The melting temperatures of carriers should be such that the solutions do not exceed ~ 70 °C, which is the maximum acceptable temperature for hard gelatin capsule shells.⁶⁸ Some of the manufacturing difficulties mentioned earlier may be en-

countered if solid dispersion products using surface-active carriers are prepared by methods other than direct filling into hard gelatin capsules; for examples, the solvent evaporation method,⁶⁹ compaction into tablets from granules,³⁷ etc.

One surface-active carrier that has commonly been used in solid dispersion for the bioavailability enhancement of drugs is Gelucire 44/14 (Gattefossé Corp., France).^{58,62–65,67} It is a mixture of glyceryl and PEG 1500 esters of long-chain fatty acids and is official in the European Pharmacopeia as lauryl macrogolglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic–lipophilic balance (HLB) value. Another surface-active carrier that generated certain interest in recent years is Vitamin E TPGS NF (Eastman, Kingsport, TN),⁷⁰ which is prepared by the esterification of the acid group of *d*- α -tocopheryl acid succinate by PEG 1000. The material has an HLB value of 13 and is miscible with water in all parts. Its melting point is, however, relatively low (38 °C) and it may require mixing with other carriers to increase melting temperatures of formulations.

In search of alternative surface-active carriers, Serajudin and co-workers^{60,71} demonstrated that a commonly used surfactant, polysorbate 80, could be used in solid dispersions by mixing it with solid PEG. Although polysorbate 80 is liquid at room temperature, it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure. As high as 50% (w/w) polysorbate 80 could be incorporated in a PEG with a lowering of <6 °C in its melting point. Even when 75% (w/w) polysorbate 80 was incorporated, PEG remained semisolid, and the lowering of the melting temperature of the PEG used was <12 °C.⁷¹ The crystalline structure of solid PEG was minimally affected by polysorbate 80 because the two compounds have low miscibility in each other. Other investigators also reported enhanced dissolution⁷² and bioavailability⁶⁵ of drugs from PEG–polysorbate carriers. Law et al.⁷³ reported a >2-fold increase in the dissolution rate of nifedipine from a PEG-based solid dispersion after incorporation of 5% (w/w) phosphatidylcholine. Increased dissolution rate of drug from solid dispersions in PEG containing varying amounts of ionic and nonionic surfactants, including sodium dodecyl sulfate and polysorbate 80, were also reported by Sjökvist et al.⁷⁴ The authors, however, pulverized the waxy material instead of filling them into hard gelatin capsules as melts.

Ease of Manufacturing—Cadé and Madt⁷⁵ and Shah et al.⁷⁶ reviewed various formulation and processing considerations for liquid-filled hard gelatin capsules. Initial formulation development studies can be conducted by filling hot solutions or dispersions into hard gelatin capsule shells manually by using pipets or by using laboratory scale semiautomatic equipment.⁷⁷ Equipment is also available to scale up the manufacturing process and for large scale manufacturing.⁷⁸ As mentioned earlier, the temperature of solutions during the filling of hard gelatin capsules should not exceed 70 °C.⁶⁸ Solutions can also be filled into soft gelatin capsules for which the solution temperature should remain <40 °C.⁷⁹ Several hard gelatin^{80,81} and soft gelatin⁸² capsule products prepared according to these techniques have been marketed in recent years.

Bioavailability Enhancement—The reports on the bioavailability enhancement by solid dispersion in surface-active carriers are promising. The human bioavailability of the poorly soluble REV5901 from a solid dispersion in Gelucire 44/14 under a fasting regimen was much higher than that of a tablet formulation even though the micronized form of drug and a wetting agent were used in the tablet.⁸³ The bioavailability of ubidecarenone in dogs from solid dispersion in Gelucire 44/14 and the Gelucire 44/14–

lecithin mixture were, respectively, two and three times higher than that of commercially available tablet.⁶³ The bioavailability of another poorly water-soluble drug, RP69698, in dogs was 4.5 times higher (27.6% versus 6%) from its solid dispersion in a PEG 3350–Labrasol–polysorbate 80 system than from an aqueous suspension in 0.5% methylcellulose.⁶⁵ Aungst et al.⁶⁷ reported that the bioavailability of an HIV protease inhibitor, DMP323, in dogs from a PEG-based formulation decreased from 49.6 to 5.2% when the dose was increased from 100 to 350 mg. No such drastic decrease in bioavailability was observed in a Gelucire 44/14-based formulation of DMP323; the bioavailability values were 68.9 and 49.5% after doses of 85 and 350 mg, respectively. The bioavailability of ritonavir (Norvir, Abbott), another poorly soluble HIV protease inhibitor (solubility <1 μ g/mL at pH >2), was enhanced by formulation as a solid dispersion in a mixture of such surface-active carriers as Gelucire 50/13, polysorbate 80 and polyoxyl 35 castor oil.⁸⁴

Special Considerations for Surfactant-Based Solid Dispersions—Solid dispersion in surface-active carriers may not be the answer to all bioavailability problems with poorly water-soluble drugs. One of the limitations of bioavailability enhancement by this method might be the low solubility of drug in available carriers.^{84,85} The desired doses of a drug cannot be solubilized and filled into hard gelatin capsules if adequate solubility in a carrier cannot be obtained. Dordunoo et al.⁶⁴ reported that the particle size of a drug in a solid dispersion remained unchanged if it is just mixed with the carrier instead of dissolving in it. On the other hand, if the drug is dissolved by heating in excess of its solubility in the carrier under normal storage condition, it may subsequently crystallize out from the solid dispersion. Either situation would defeat the purpose of bioavailability enhancement of poorly water-soluble drugs by solid dispersion, as described in Figure 1.

The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott) from the market.⁸⁶ The crystallization of drug adversely influenced the dissolution of the ritonavir capsule, and the product was switched to a thermodynamically stable solution formulation. Aungst et al.⁶⁷ also stressed the importance of drug solubility in carriers in the development of capsule formulations. They prepared high-dose formulations of a water-insoluble HIV protease inhibitor by dissolving it in carriers at an elevated temperature only, and the formulations were used for bioavailability testing in dogs within 24 h of preparation when no crystallization occurred. The authors cautioned that precipitation of drug could occur upon storage at room temperature over a longer period of time, and that lowering of drug concentration in the carrier would be necessary to ensure long-term physical stability of the formulation.

To ensure that a drug would not crystallize out of solid dispersion at the desired storage temperature, it is important to screen the drug solubility in different carriers at such a temperature. However, no practical method for determining or estimating drug solubility in a carrier at a relatively low temperature, where the carrier exists in a solid state, has been reported in the literature. The relative solubility of a drug in different carriers may be determined by equilibrating the drug at an elevated temperature where all the carriers exist in a liquid state.⁶⁷ If the solubility of a drug in a carrier at an elevated temperature is much higher than the concentration required for solid dispersion, an accurate estimation of solubility at room temperature might not be necessary and a reasonable assumption might be made that the drug would not precipitate out. When a better estimation of solubility is needed, one practical

approach is the determination of solubility–temperature relationship of drug in a chemically related carrier that exists as liquid at a wider range of temperature. For example, for the purpose of estimating the solubility of a drug in a solid PEG at room temperature, the solubility may be determined at an elevated temperature where the PEG exists in a liquid state. Then the solubility of drug at a lower temperature may be estimated from the solubility–temperature relationship in a related vehicle, PEG 400, which remains liquid at a wider range of temperature. This method assumes, however, that similar temperature–solubility relationships for the drug would exist in both PEGs and that the relationship would not change when one of them solidifies. The solubility may also be estimated by microscopic examination of solid solutions with increasing drug concentration for any possible crystallization of drug, assuming that the drug does not exist as a separate amorphous phase and the crystallization occurs in a relatively short period of time. A similar microscopic technique was used for determining the solubility of diazepam in liquid crystalline phases of lecithin.⁸⁷

Another possible limitation of the use of surface-active carrier reported by Aungst et al.⁶⁷ is that the bioavailability of a drug may vary depending on the amount of carrier administered along with it. This variation is because different amounts of a surface-active carrier may have different solubilization or dispersion effects on a drug in the gastrointestinal fluid. Serajuddin et al.^{58,60} reported a method whereby the rate and efficiency of dispersion of drug in aqueous media from different formulations can be studied.

In addition to the solubility, careful attention must be given to the drug-to-carrier ratio in the successful development of a formulation. When the solubility of a particular drug is relatively low, a high drug-to-carrier ratio is necessary to deliver it in a solubilized state, and, therefore, the dose has to be low if it is desired that the total dose is delivered as a single unit. As mentioned earlier, any attempt to supersaturate the drug in solid dispersion to reduce drug-to-carrier ratio may lead to stability problems and, ultimately, to product failure.

Attention should also be given to optimization and validation of the manufacturing process. It is not only that the physicochemical properties of the drug is affected by the cooling rate, the properties of carriers in a solid dispersion might also be influenced by the solidification rate of the product.^{88,89} The implication of this observation on bioavailability and stability of drug product is not known.

Future Prospects

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical, and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drugs in melted carriers and the filling of the hot solutions into hard gelatin capsules. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and, as a result, the bioavailability of solid dispersions are not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts

of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation.

One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may be the inadequate drug solubility in carriers, so a wider choice of carriers will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention must also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP3-based drug metabolism and *p*-glycoprotein-mediated drug efflux, will require careful consideration.⁹⁰

In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms. Although a review of literature on this aspect of solid dispersion is outside the scope of the present article, it may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule-filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use,⁹¹ it is expected that the research in these two areas will progress simultaneously and be complementary to each other.

Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market,⁸⁶ so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability. Possible drug–carrier interactions must also be investigated.

Although, as mentioned earlier, the direct filling of solid dispersion into hard gelatin capsules is a relatively simple process, there are very limited reports on the scale up of the technology. Further studies on scale up and validation of the process will be essential. Many problems and challenges still remain with solid dispersion systems. Nevertheless, as a result of recent breakthroughs, it will continue to be one of the exciting frontiers of drug development.

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