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Abstract
Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. This article reviews the various preparation techniques for solid dispersion and compiles some of the recent technology transfers. The different types of solid dispersions based on the molecular arrangement have been highlighted. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier, solvent and methods of physicochemical characterization, along with an insight into the molecular arrangement of drugs in solid dispersions are also discussed. In this review, it is intended to discuss the recent advances related on the area of solid dispersions.

Key Words
Solid dispersion, carrier, solubility, bioavailability.

Introduction
Oral drug delivery is the simplest and easiest way of administering drugs.1,2 Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration.3,4 In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration,4,5 which can detract from the drug’s inherent efficacy.6,7 Moreover, most promising NCEs, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window.8,9 Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability.8,10 Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs.6,11,12 Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects.6,11,13,14 Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs.15

Definition of Solid Dispersion
The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.16

Advantages of Solid Dispersion
1. Particles with reduced particle size
Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

2. Particles with improved wettability
A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid
and bile salts. When used, can significantly increase the wettability of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

3. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

4. Drugs in amorphous state

Poorly soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.  

Disadvantages of Solid Dispersion

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization. Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during in vivo performance.

Another drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

Categories of Solid Dispersions

A. Simple eutectic mixtures

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other (Fig. 1). Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

B. Solid solutions

a) According to their miscibility

I. Continuous solid solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

II. Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram is shown in Fig. 2 show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it has been suggested by Goldberg that the term ‘solid solution’ should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two
components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.

b) According to the way in which the solvate molecules are distributed in the solvendum

I. Substitutional crystalline solid solutions

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. A substitutional crystalline solid dispersion is depicted in Fig. 3. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

I. Interstitial crystalline solid solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice (Fig. 4). As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

I. Amorphous solid solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (Fig. 5). Using griseofulvin in citric acid, Chiou and Riegelman [30] were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature.

C. Glass solutions and glass suspensions

Chiou and Riegelman first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The familiar term glass however, can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature \( T_g \). On heating, it softens progressively and continuously without a sharp melting point.

D. Other Categories

a) Non-Self-Emulsifying SDs (NSESs)

NSESs refer to SDs composed of carriers or other agents that have no self-emulsifying properties. Hydrophilic carriers are more favorable in these systems, for example, polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), HPMC, cyclodextrins, urea and mannitol. These carriers are crystalline or amorphous, but the amorphous form is usually preferable because the drug has a better chance to be molecularly dispersed within the amorphous carrier, creating the amorphous SDs for the maximized solubilization of drugs. In contrast, when the drug remains in the crystalline state within the crystalline carriers, the drug in the SDs is not satisfactorily soluble in the carrier, but the drug release rate is still increased—in this case, because of the partial amorphousness of drugs. The enhancement of drug release and bioavailability from these SDs is also attributed to the reduced particle size and the better wettability of the drug rather than to structural changes in drug crystallinity. Additionally, the rapid release of drug can be attributed to the rapid dissolution of the carrier. The preparation method for NSESs can be either the solvent method or the melting method, depending on the physicochemical properties of the drug and carrier.

b) Self-Emulsifying SDs (SESDs)

In contrast to NSESs, the carriers in SESDs systems have surface activity or self-emulsifying properties. In the SESD preparation, the carriers are usually melted at elevated temperatures, and the drugs are then dissolved in the molten carriers.
These surface-active agents, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions, adsorb drugs onto the surfaces or interfaces of a system, thereby altering the surface or interfacial free energy to reduce the surface and the interfacial tension, through which the dissolution of drug can be increased by preventing the formation of any water-insoluble surface layer. The high surface area of the dissolved vehicle would further facilitate the dissolution of the drug via the finely divided state of the emulsion droplets. Surface-active agents including Gelucire®, Pluronic®, Compritol®, Labrasol®, Transcutol® and tocopheryl polyethylene glycol 1000 succinate are carriers commonly used in the preparation of SESDs. Furthermore, these carriers, depending on the type of dosage forms, can improve the solubility or stability of the drug in the liquid preparation, stabilize and modify the texture of semisolid preparations, or alter the flow properties of the final tablet dosage form. Compared to the NSESDs, in which the dispersed drug may be more prone to dissociation from the water soluble matrix, the physical state of drug in SESDs can be improved as long as a continuous drug surface layer is largely maintained by the molecular dispersion of drug in the carrier to form a solid solution. The SESDs are usually filled into hard capsules as hot-melts, which then solidify at cool or room temperature, or are mixed with adsorbents and other free-flowing excipients for subsequent tablet compression.

**Selection of the Carrier**

The selection of the carrier has the influence on the dissolution characteristics of the dispersed drug, since the dissolution rate of one component from the surface is affected by the other component in a multiple component mixture. Therefore, a water-soluble carrier results in a faster release of the drug from the matrix. A poorly soluble or insoluble carrier leads to slower release of a drug from the matrix. If the active drug present is a minor component in the dispersion, faster release of a drug can be achieved from matrix. The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

1. Be freely water-soluble with intrinsic rapid dissolution properties.
2. Be non-toxic and pharmacologically inert.
3. Be heat stable with a low melting point for the melt method.
4. Be soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
5. Be able to preferably increase the aqueous solubility of the drug and
6. Be chemically compatible with the drug and not form a strongly bonded complex with the drug.

**Methods of Preparation**

**Melting Method**

The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast-release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved. Such a technique was subsequently employed with some modification by Goldberg et al. and Chiou and Riegelman. To facilitate faster solidification, the homogeneous melt was poured in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. The solidified masses of drug-polyethylene glycol polymer systems were often found to require storage of 1 or more days in a dessicator at ambient temperatures for hardening and ease of powdering. Some systems, such as griseofulvin and citric acid, were found to harden more rapidly if kept at 37 °C or higher temperatures. The main advantages of this direct melting method are its simplicity and economy. In addition, a super saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. Similarly, a much finer dispersion of crystallites was obtained for systems of simple eutectic mixtures if such quenching techniques were used. The disadvantage is that many substances, either drugs or carriers, may decompose or evaporate during the fusion process at high temperatures. For example, succinic acid, used as a carrier for griseofulvin, is quite volatile and may also partially decompose by dehydration near its melting point. However, this evaporation problem can be avoided if the physical mixture is heated in a sealed container. Melting...
under vacuum or a blanket of an inert gas such as nitrogen may be employed to prevent oxidation of the drug or carrier\textsuperscript{44}. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system\textsuperscript{45}. By proper control, the melting point (the temperature at which the mixture completely melts) of a binary system may be much lower than the melting points of its two components. Under such a condition, this simple melting method can still be used to prepare solid dispersions, even if the pure drug may undergo decomposition at or near its melting point. This principle was used to prepare solid dispersions of steroids and a cardiac glycoside in polyethylene glycol 6000\textsuperscript{46} and that of griseofulvin in pentaerythritol\textsuperscript{59}.

**Hot melt extrusion**

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder are a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding\textsuperscript{47,52,18}. Hot-melt extrusion is the process in which a powder blend of drug and carrier is transferred by a rotating screw through a heated barrel of an extruder and then the melt is pressed through a die to obtain a product of uniform shape. A critical amount of force must be applied for dispersing and mixing of the powder blend, breaking the aggregates of the minor drug particles. The single screw extrusion, however, does not provide the high mixing capability. Hence, a twin-screw machine with its co rotating or counter-rotating screws is the preferred approach for the production of pharmaceutical formulations\textsuperscript{61}.

**Solvent method**

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\textsuperscript{53}. 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. Chio and Riegelman used 500 ml of ethanol to dissolve 0.5g 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\textsuperscript{30,46}. To minimize the volume of organic solvent necessary, Usui et al. dissolved a basic drug in a hydro alcoholic mixture of 1 N HCl and methanol, with drug-to co solvent ratios ranging from 1:48 to 1:20, because as a protonated species, the drug was more soluble in the acidic co solvent 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. 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. 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\textsuperscript{53,54}. Simonelli et al. evaporated ethanolic solvent on a steam bath and the residual solvent was then removed by applying reduced pressure. Chio and Riegelman 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, spray-drying, spraying on sugar beads using a fluidized bed-coating system, lyophilization, 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\textsuperscript{55}. 

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Supercritical Fluid Method
Supercritical CO2 is a good solvent for water insoluble as well as water soluble compounds under suitable conditions of temperature and pressure. Therefore, supercritical CO2 has potential as an alternative for conventional organic solvents used in solvent based processes for forming solid dispersions due to its favourable properties of being nontoxic and inexpensive. The process developed by Ferro Corporation consists of the following steps:

- Charging the bioactive material and suitable polymer into the autoclave.
- Addition of supercritical CO2 under precise conditions of temperature and pressure, that causes polymer to swell;
- Mechanical stirring in the autoclave; and
- Rapid depressurization of the autoclave vessel through a computer controlled orifice to obtain desire particle size. The temperature conditions used in this process are fairly mild (35–75°C), which allows handling of heat sensitive biomolecules, such as enzymes and proteins.56,57

Kneading method
In the kneading method, the drug and polymer are triturated using a small volume of solvent (the minimum amount of organic solvent possible) to obtain a thick paste, which is needed for a determined time and then dried in an oven if temperature does not affect the system’s characteristics.

Cogrinding method
In the cogrinding method, the drug is triturated with a minimum quantity of the solvent in a glass mortar until it is dissolved. The carrier is then added, and the suspension is triturated rapidly at room temperature until the solvent is evaporated. The controlled drug release can be attributed to the amount of polymer, which induces a longer diffusional path and higher viscosity, thus releasing the drug over a longer time at a higher amount. It can also be attributed to the low permeability of the polymer, which poses a significant hindrance to fluid penetration and passive drug diffusion. However, there has been a tendency to restrict the use of organic solvents in recent years.

MeltDose
However, it seems that this technology has some disadvantages. The authors of the proprietary technology MeltDose® described some drawbacks of the hot-melt extrusion method, such as up-scaling problems, chemical instability and the use of non conventional pharmaceutical equipment. MeltDose is suggested to be a one-step industrial process for manufacturing SDs in which the drug is incorporated in a meltable vehicle and the mixture is subsequently sprayed on a particulate carrier such as lactose by fluid bed equipment. Granule particle size is controlled by the product temperature and by optimization of the feed rate and product temperature. The property of granules makes it applicable for direct tabletting without additional processing steps, except for blending with a lubricant. Moreover, the technology is purported to be easily scaled up to manufacturing scale. The technology may be combined with a series of standard formulation techniques used for controlled-release formulations, such as enteric coating, extended release or slow release. Melt-Dose® has proven to be an effective technology for producing SDs of a number of poorly soluble drugs because it eliminates the drawbacks limiting the use of the SD formulations in drug development. The process may be carried out in a controlled atmosphere (nitrogen) to avoid the degradation of drugs or polymers that might undergo oxidation.

Quasi-Emulsion Solvent Diffusion Method
Additionally, the novel quasi-emulsion solvent diffusion method developed by Kawashima et al. to prepare the CR microspheres of ibuprofen with acrylic polymers has been applied to prepare CR microspheres containing SD structure. Currently, this technique is used more frequently for the SD preparation of water-insoluble drugs to simplify the manufacturing process and has high potential for improving drug bioavailability. This method employs three solvents:

1. a good solvent that dissolves the drug
2. a poor solvent in which the drug is insoluble
3. a bridging liquid as the solvent that dissolves the drug

Bridging liquid is immiscible with the poor solvent and miscible with the good solvent. When the bridging liquid and good solvent containing the drug are poured into the poor solvent under agitation, quasi-emulsion droplets of the bridging liquid or good solvent form in the poor solvent and induce crystallization of the drug, followed by agglomeration. The solidified droplets can be
recovered by filtration, washed with water and dried to obtain the final products.61

APPLICATIONS OF SOLID DISPERSIONS
1. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
2. To stabilize unstable drugs against hydrolysis, oxidation, recrimation, isomerisation, photo oxidation and other decomposition procedures.
3. To reduce side effect of certain drugs.
4. Masking of unpleasant taste and smell of drugs.
5. Improvement of drug release from ointment creams and gels.
6. To avoid undesirable incompatibilities.
7. To obtain a homogeneous distribution of a small amount of drug in solid state.
8. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
9. To formulate a fast release primary dose in a sustained released dosage form.
10. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
11. To reduce pre systemic inactivation of drugs like morphine and progesterone.16, 17, 32, 33, 34, 59, 60

Conclusion
Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Because of solubility problem of many drugs the bio availability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs.

References
36. Zbid. 1966, 55,482.

![Fig. 1 Phase diagram for a Eutectic system](image1.png)
![Fig. 2 Phase diagram for a discontinuous solid solution](image2.png)
![Fig. 3 Substitutional crystalline solid solutions](image3.png)
![Fig. 4 Interstitial crystalline solid solutions](image4.png)
Fig. 5 Amorphous solid solutions