Solid dispersion: A promising technique to enhance solubility of poorly water soluble drug

Anshu Sharma1*, C.P. Jain2

Abstract
Poorly water soluble compounds have solubility and dissolution related bioavailability problems. The present review deals in detail about solid dispersion technology and its manufacturing techniques at laboratory and industrial level. This highlights about various hydrophilic polymers used in this technique to enhance solubility of poorly soluble drugs. It also discusses about modern characterization technique to characterize solid dispersion. In this review, it is intended to discuss the recent advances related on the area of solid dispersion technology.

Keywords: Solid dispersion; Carriers; Solubility; Dissolution; Bioavailability.

Introduction
The solubility of a drug is a key determinant of its oral bioavailability and permeability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry [1, 2]. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid dispersion.

Scientists gave different explanations of Solid dispersion. Chiou and Riegelman [3] defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”. Sekiguchi and Obi [4] suggested that the drug presented in a eutectic mixture in a microcrystalline state, after few years Goldberg et al.[5] reported that all drug in solid dispersion might not necessarily be present in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution.

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 by melting or solvent method. Therefore, based on their molecular arrangement, different types of solid dispersions (SDs) can be distinguished. They are described in Table 1.
### Table 1: Classification of solid dispersions in six subtypes.

<table>
<thead>
<tr>
<th>Solid Dispersion</th>
<th>Type</th>
<th>Matrix*</th>
<th>Drug**</th>
<th>Remarks</th>
<th>No. of phases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Eutectics</td>
<td>C</td>
<td>C</td>
<td>the first type of solid dispersions prepared</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>Amorphous precipitations in crystalline matrix</td>
<td>C</td>
<td>A</td>
<td>rarely encountered</td>
<td>2</td>
<td>6, 7</td>
</tr>
<tr>
<td>III</td>
<td>Solid solutions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>miscible at all compositions, never prepared</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Discontinuous solid solutions</td>
<td>C</td>
<td>M</td>
<td>partially miscible,</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Substitutional solid solutions</td>
<td>C</td>
<td>M</td>
<td>molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed</td>
<td>1 or 2</td>
<td>8, 9</td>
</tr>
<tr>
<td></td>
<td>Interstitial solid solutions</td>
<td>C</td>
<td>M</td>
<td>drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinous. Example: Drug in helical interstitial spaces of PEG.</td>
<td>2</td>
<td>3, 10</td>
</tr>
<tr>
<td>IV</td>
<td>Glass suspension</td>
<td>A</td>
<td>C</td>
<td>particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix</td>
<td>2</td>
<td>3, 11</td>
</tr>
<tr>
<td>V</td>
<td>Glass Suspension</td>
<td>A</td>
<td>A</td>
<td>particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type</td>
<td>2</td>
<td>3, 11</td>
</tr>
<tr>
<td>VI</td>
<td>Glass solution</td>
<td>A</td>
<td>M</td>
<td>requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

*: A: matrix in the amorphous state  
C: matrix in the crystalline state  
**: A: drug dispersed as amorphous clusters in the matrix  
C: drug dispersed as crystalline particles in the matrix
Mechanism of Dissolution
Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight, composition, drug crystallinity, particle porosity and wettability, when successfully controlled can produce improvements in bioavailability [13,14].

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. A high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability [15, 16].

Particles with improved wettability
A strong contribution to the enhancement of drug solubility is related to the drug wettability [17]. It has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; hence improved wetting may lead to reduced agglomeration and increased surface area [18].

Particles with higher porosity
Particles in solid dispersions have been found to have a higher degree of porosity [19]. 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 [20].

Drugs in amorphous state
Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility [21, 22] 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 [23]. 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 [14, 16].

Disadvantages OF Solid Dispersions
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 [24-26]. 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 [27]. 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 [28]. 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.

Pharmaceutical Applications of Solid dispersion:
The pharmaceutical applications of solid dispersions technique are numerous. They may be employed-
1. To enhance the absorption of drug;
2. To obtain a homogeneous distribution of a small amount of drug in solid state;
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.;
4. To dispense liquid or gaseous compounds;
5. To formulate a fast release priming dose in a sustained release dosage form;
6. To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier;
7. To reduce side effects-(a) the binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex, (b) the damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound;
8. To mask unpleasant taste and smell. The very unpleasant taste of anti-depressant famoxetine hindered the development of oral liquid formulations. The bitter taste was greatly suppressed when the solid complex of famoxetine was formulated as aqueous suspension;
9. To convert liquid compounds into formulations. Liquid drugs can be manufactured as solid drug formulations such as powders, capsules or tablets e.g., unsaturated fatty acids, essential oils, nitroglycerin, benzaldehyde, prostaglandin, clofibrate etc.

Method of Preparation
Various preparation methods for solid dispersions have been reported in literature. Some laboratory and industrially feasible methods are summarized here:

Fusion method
The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Sekiguchi et al. [4] were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. A common adaptation to the melting phase consists of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, therefore reducing, the process temperature. To cool and solidify the melted mixture, several processes such as ice bath agitation, stainless steel thin layer spreading followed by a cold draught, solidification on petri dishes at room temperature, inside a desiccator, spreading on plates placed over dry ice, immersion in liquid nitrogen or stored in a desiccator were used. After cooling, the mixture must be pulverized regarding its handling [29-31].

The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. However, the use of high temperatures, and the fact that several drugs can be degraded by the melting process, can be a limitation of this method. The incomplete miscibility between drug and carrier that may occur, because of the high viscosity of a polymeric carrier in the molten state, is another limitation of this process [32-34]. To avoid the melting method limitations, several modifications, like hot-stage extrusion, Meltrex™ or melt agglomeration were introduced to the original method.

Solvent method
The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties [35, 36].

With the discovery of the solvent method, many of the problems associated with the melting method were solved. For example, it was then possible to form solid dispersions of thermolabile substances. Likewise, many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could be now considered as carrier possibilities. As a result, for
many years the solvent method was the method of choice for polymer-based systems.

Using the solvent method, the pharmaceutical engineer faces many challenges. The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. Identification of a common solvent for both drug and carrier can be problematic and complete solvent removal from the product can be a lengthy process. Moreover subtle alterations in the concentrations used for solvent evaporation may lead to large changes in the product performance. In addition large volumes of solvents are generally required which can give rise to toxicological problems.

With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent-based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the preparation of solid dispersions. Many investigators studied solid dispersion of felodipine [37] meloxicam [38], naproxen [39, 40], atenolol [41], and nimesulide [42] using solvent evaporation technique.

**Hot melt extrusion**

Hot-stage extrusion (HME) consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is then collected after cooling at room temperature and milled [43-45]. A reduction in processing temperature can be achieved by the association of hot-stage extrusion with the use of carbon dioxide as a plasticizer [46, 47], which broadens the application of hot-stage extrusion to thermally labile compounds. Solid dispersions of para-amino salicylic acid/ethylcellulose [48], itraconazole/ PVP [49] and itraconazole/ethylcellulose [50] were successfully prepared by this technique. Moreover, it was observed that solid dispersions of itraconazole/inutec SPI prepared by hot-stage extrusion presented itraconazole in a fully glassy state, whereas it was only partially glassy in solid dispersions prepared by spray drying [51].

HME also offers several advantages over traditional pharmaceutical processing techniques including the absence of solvents, few processing steps, continuous operation, more possibility of the formation of solid dispersions and improved bioavailability [52].

An amorphous solid dispersion of itraconazole with HPMC was formed from milled melt extrudate and resulted in a significantly increased dissolution rate compared with the physical mixture; the formulation was found chemically and physically stable for periods in excess of 6 months [53, 54]. The tablets formed by compressing milled melt-extruded glassy powder with additional excipients showed high oral bioavailability [55].

**Electrostatic spinning method**

In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. Electrospun samples dissolved dependent on the type of formulation and the drug:polymer ratio. The technique has been successfully used in the pharmaceutical industry for the preparation of solid dispersions [56-58].

Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and nonbiodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct
incorporation of the materials into a capsule. Itraconazole/HPMC nanofibers have been prepared by using this technique [59, 60].

**Direct capsule filling**

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. The filling of hard gelatin capsules has been feasible in molten dispersions of triamterene-PEG 1500 using a Zanasi LZ 64 capsule-filling machine (Zanasi Co, Bologna, Italy) [61, 62]. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross-contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug [63]. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (eg, polysorbate 80 with PEG, phosphatidylcholine with PEG [64, 65]. The temperature of the molten solution should not exceed above 70°C because it might compromise the hard-gelatin capsule shell.

**Supercritical fluid (SCF) process**

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power [66, 67]. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5-2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specialising in particle engineering via SCF technologies for particle size reduction and solubility enhancement [68, 69].

Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), solution enhanced-dispersion by SCF (SEDS), supercritical antisolvents processes (SAS) and aerosol supercritical extraction system (ASES) [70, 71].

It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. SCF technology offers tremendous potential, as it is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.

**Lyophilization technique**

Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion [72]. This technique was proposed as an alternative technique to solvent evaporation. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. Betageri et al. [73], Topalogh et al. [74], Badry et al. [75] and Fathy et al. [76] have successfully
investigated the potential applications of lyophilization technique using glyburide, ketoprofen, meloxicam, amylobarbitone in solid dispersion manufacturing.

An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum. Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration.

Drooge et al. [77] suggested spray freeze-drying process to produce 9- tetrahydrocannabinoin containing inulin based solid dispersions with improved incorporation of tetrahydrocannabinoin in inulin.

Spray drying
Today, spray drying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive than freeze-drying. It is an established method that is initiated by atomizing suspensions or solutions into fine droplets followed by a drying process. The process allows production of fine, dust free powder as well as agglomerated one to precise specifications. The operating conditions and dryer design depends upon the drying characteristics of the product and require powder specifications [78-80].

The spray drying technique is a useful method to obtain spherical particle and narrow distribution. The role of porous materials such as calcium silicate, controlled pore glass and porous cellulose is appreciated to formulate solid dosages forms because they confer special characteristics such as decrease of melting point and a decrease in the crystallinity of drug entrapped in pores. In addition, porous material controls polymorphs and stabilizes meta-stable crystals in solid dispersions under sever storage conditions. Moreover, porous silica has been reported to improve solubility and dissolution rates of indomethacin and tolbutamide [81, 82]. The frequent use of the organic solvent in spray drying pose problems such as residues in products, environmental pollution and operational safety as well as corporate problems such as capital investment.

Solid dispersion of loperamide and PEG 6000 were prepared by this technique [83]. The prepared SD(s) exhibited higher dissolution rates than that of pure crystalline loperamide. Chouhan et al. [84] studied the suitability of this technique for preparation of SD(s) of glibenclamide with polyglycolized glycerides. This study revealed the improvement in solubility, dissolution rates and in therapeutics efficacy of glibenclamide in SD(s).

Carriers in solid dispersion
Carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance dissolution of drugs. The carriers which have been reported in literature are described in detail below.

Polyethylene glycol
Polyethylene glycols (PEGs) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200 ± 3,00,000. Their solubility in water is generally good, but decreases with MW. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 65°C in every case (e.g. the m.p. of PEG 1000 is 30-40°C, the m.p. of PEG 4000 is 50-58°C and the m.p. of PEG 20,000 is 60-63°C) [85]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Even the
dissolution rate of a relatively soluble drug like carbamezapine can be improved by formulating it as a solid dispersion in PEG 6000.

PEGs of MW 4000-6000 are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is still very high, but hygroscopy is not a problem and the melting points are already over 50°C. If a PEG with too low a MW is used, this can lead to a product with a sticky consistency that is difficult to formulate into a pharmaceutically acceptable product [86].

Ozkan et al. [87] reported increasing solubility of etodolac with PEG 6000 as a carrier by melting method. Similarly Dehghan and Jafar [88] studied meloxicam solid dispersions prepared by physical mixing, co-grinding and solvent evaporation methods with PEG 6000. The enhanced dissolution rate of meloxicam by solid dispersion technique may be due to increased wettability and hydrophilic nature of carrier.

Further drugs which exhibit elevated release rates when formulated as PEG 6000 solid dispersions include ofloxacin [89], silymerin [90], gliclazide [91], dapsone [92], mebendazole [93], Cisapride [94], Nitrendipine [95], oxazepam [96], valdecoxib [97], isosorbide dinitrate [98], zolpidem [99], piroxicam [100], fenofibrate [101], glibenclamide [102], ketoprofen [103]. PEGs with higher MW have also been use with success e.g. products containing PEG 8000 [104] and PEG 10,000 [105] showed enhanced dissolution rates compared to the pure drug.

Poly vinyl pyrrolidone
Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3,000,000. These can be classified according to the K value [106]. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid [107]. The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer and viscosity lowers with increasing chain length.

Solid dispersions of praziquantel (PZQ) containing varying concentrations of PVP with different MW (3000, 11,000 and 34,000) were prepared. The solubility of PZQ in the coprecipitate was greater when PVP of a smaller molecular weight was used [108]. An enhancement of 6.15-fold in dissolution rate of ipriflavone (IP) solid dispersion [109] was noted with PVP K-30 as that of IP alone and 40 fold increase with piroxicam [110] when PVP K 17 is used.

Further drugs which exhibit elevated release rates when formulated as PVP solid dispersions include diflunisal [111], nifedipine [112], tanshinone [113], cefuroxime axetil [114], flunarizine [115], daidzein [116], nitrendipine [117], ketoprofen [118], bicalutamide [119], quercetin [120], lansoprazole [121].

Urea
Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 in 1 and it also exhibits good solubility in many common organic solvents. In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea [4]. Similarly, Goldberg et al. [5] reported faster dissolution rates of chloramphenicol when prepared with urea as the carrier. Although urea is not often used as a carrier these days, it has been recently shown that the dissolution rate of the poorly soluble compound ofloxacin can be improved by more than three fold by incorporating it in coevaporate.
with urea [122]. In the case of Rofecoxib [123] the release rate from urea dispersions was faster than from other carriers studied, including PEG 4000. A increase in the dissolution rate of piroxicam [124] has also been achieved with urea; however, in this case PEG 4000 was far more efficient. Maheshwari [125] reported solubility enhancement by using urea as a hydrotropic agent. Verma investigated increased dissolution of flurbiprofen with urea and xylitol [126].

### Sugars

Although sugars and related compounds are highly water soluble but few sugars have toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare coevaporates. Despite these drawbacks, several attempts to prepare solid dispersions using sugars and their derivatives have been reported.

Lactose is useful as a carrier for the production of solid dispersions of drugs having a primary amide group in their structures like carbamazepine or ethenzamide prepared by melting and rapid cooling showed marked increase in dissolution same results were shown in study with naproksen [127, 128].

Chitosan, a derivative of the polysaccharide chitin which is formed by deacetylation at the N position, has also been used as a carrier in solid dispersions. Both chitosan and its salt form, chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder [129]. In solid dispersion with 1:1 ratio ofloxacin to chitosan, showed as the best carrier for drug release [130]. Similar results were found with fenofibrate [131], oxazepam [132] and miconazole [133].

Mannitol, which has a melting point of 165-168°C and decomposes only above 250°C, can be employed in some cases to prepare dispersions by the hot melt method. Improved release characteristics have been reported for sorbitol dispersions of several compounds, including nitrofurantoin [134], prednisolone [135], ofloxacin [136] and ursodeoxycholic acid [137]. In most of these cases, other carriers produced better results. Interestingly, nitrofurantoin showed better release from sorbitol than mannitol dispersions. Indeed, a dispersion of prednisolone in sorbitol released the drug faster than all other carriers tested, including PEG, PVP, urea and mannitol [138].

### Emulsifiers

The release behaviour of many drugs can also be improved through the use of emulsifying agents. Two mechanisms are possible here: improvement of wetting characteristics and solubilization of the drug. Owing to their potential toxicity problems, such as damage to mucosal surfaces, they are used in combination with another carrier. For example, the enhanced release of mefenemic acid from solid dispersions, using PEG 6000 with tween 20 [139]. An increase in 7 fold in solubility observed when solid dispersions of nitrendipine were prepared by using a melting method with PEG 6000 and polysorbate 80 as carriers [140]. The fenofibrate solid dispersion tablets prepared by solvent-melting method using PEG 4,000 and sodium lauryl sulfate has showed increased release [141]. Shokri and Azami proved the effect of anionic (SLS), cationic (CTAB) and nonionic (Myrj 52) surfactants as carriers on enhanced dissolution rate of oxazepam. Surfactants are suitable carriers for low dose and very low water soluble drugs [142].

Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). Because of their amphiphilic structure, the polymers have surfactant properties that make them useful in industrial applications. Among other things, they can be used to increase the water solubility of
hydrophobic and oily substances or otherwise increase the miscibility of two substances with different hydrophobicities. For this reason, these polymers are commonly used in industrial applications, cosmetics and pharmaceuticals.

Kwon and Kim [143] suggested pluronic F 127 polymeric micelles could improve the oral bioavailability of genistein. Badry and Fathy used pluronic F 98 for dissolution enhancement of piroxicam [144]. Similar results like increased solubility and enhanced bioavailability have been showed by nifedipine and ebselen [145,146].

Chen et al. improved the dissolution and bioavailability of ABT-963, a poorly water-soluble compound by preparing solid dispersion using Pluronic F-68 as a carrier by evaporation and hot melt method [147].

The recently used surface-active carrier is Gelucire® 44/14 and other grades of Gelucire®. The carriers are prepared to have a high melting point but not more than 70°C so as to compatible to be filled in hard gelatin capsule. The grades of Gelucire® is denoted by different number like 44/14 and 13, in that first digit denotes the melting point of carrier and second digit denote HLB value of carrier. Gelucire® 44/14 is a mixture of glyceryl and PEG-1500 ester of long-chain fatty acid and is official in European pharmacopoeia as a lauryl macrogolglycerides [148].

Dordunoo et al. [149] studied the effect of Gelucire® 44/14 for improving the solubility of temazepam in comparison with various poly ethylene glycol and shown large increase in its water solubility. Enhanced dissolution was observed with lornoxicam [150], tiaprofenic acid [151], thicarboxanilide UC-781 [152] and carbamazepine [153] when gelucire 44/14 is used as surfactant alone and with other carriers.

Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important for the emulsification of fats and oils in the diet. Like other surfactants, they enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate. Stoll et al. [154] demonstrated the ability of bile salts such as cholic acid, deoxycholic acid and lithocholic acid to improve not only the release but also the sedative effects of reserpine when given as a coevaporate. Likewise, the release of hydrocortisone can be enhanced by formulation as a solid dispersion in cholesterol and various cholesterol esters [155].

**Polyacrylates and polymethacrylates**

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mostly used in coatings to modify the release of the drug from the dosage form. Commonly they are referred by the trade name Eudragit [156]. Among the eudragits eudragit E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pH values, while eudragit L can be used when it is desirable to avoid release in the stomach. Jun and Jeong observed improved dissolution of atorvastatin calcium with eudragit E100 as a carrier [157].

**Cellulose derivative**

Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by β-1,4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl- (MC), hydroxypropyl (HPC), hydroxypropylmethyl (HPMC) and many other semi-synthetic cellulosics. A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP) [158].
Suspension formulated employing paracetamol-HPMC solid dispersions gave highest improvement in the dissolution rate and dissolution efficiency of paracetamol [159]. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nilvadipine [160] and benidipine [161], Carbamezapine [162] and cisapride [163]. Yuasa et al. [164] carried out extensive studies of the influence of the chain length and proportion of HPC in the solid dispersion on the release behaviour of flurbiprofen. The release rate improved as the proportion of HPC was increased and when lower molecular weight HPCs were used as the carrier.

Characterization of Solid Dispersion
There have been several reports on the analysis of solid dispersions. A variety of techniques, such as XRPD, NMR, Raman and IR have been used to identify the crystal form in a wide selection of dosage forms, including tablets, capsules, ointments, suppositories and microspheres [165]. A small selection of the available literature will be discussed here.

Powder Xray diffraction
As a consequence of the importance of solid drug substance characterization, analytical tools such as X-ray diffractometry are usually employed in the pharmaceutical field. The detection of crystalline phases in mixed systems can be analyzed by powder X-ray diffraction. However, too much crystallinity causes brittleness. The crystallinity parts give sharp narrow diffraction peaks and the amorphous component gives a very broad peak. The ratio between these intensities can be used to calculate the amount of crystallinity in the material [166-170].

Differential scanning calorimetry (DSC)
DSC is a well-known technique that measures heat flow into or out of a material as a function of time or temperature. Crystallinity can be determined with DSC by quantifying the heat associated with melting (fusion) of the material. Glass transitions may occur as the temperature of an amorphous solid is increased. This is due to the sample undergoing a change in heat capacity; no formal phase change occurs. As the temperature increases, an amorphous solid will become less viscous. At some point the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature (Tc). This transition from amorphous solid to crystalline solid results in an exothermic peak in the DSC signal. As the temperature increases the sample eventually reaches its melting temperature (Tm). The melting process results in an endothermic peak in the DSC curve.

The exact nature of the thermal transitions has to be determined with complementary methods such as microscopic observations, thermogravimetry, X-ray diffraction or spectroscopic techniques to distinguish [171-175].

Hot stage microscopy
Hot stage microscopy is one of the oldest and most straightforward methods for studying phase transitions in crystals. Varying the temperature of a substance while viewing it under a microscope, often through crossed polarizers, provides a wealth of information about melting or recrystallization behavior as well as solid-state transformations. This technique also allows the detection of solvates by observing the evolution of a gas or liquid from a crystal. Novel polymorphs can be generated in this experiment either by high temperature transition of one form to another or by crystallization from the melt. Coupling hot stage microscopy with vibrational spectroscopy or DSC can further expand the utility of this method [176, 177].

Macroscopic techniques
Macroscopic techniques measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and dynamic mechanical analysis (DMA) determine the module of the elasticity and
Viscosity and thus affected by the degree of crystallinity.

**Nuclear magnetic resonance spectroscopy**
Solid-state nuclear magnetic resonance (SS-NMR) spectroscopy can be used to investigate polymorphism by probing the environments of atoms in the solid state; non-equivalent nuclei will resonate at different frequencies and these changes in chemical shift can often be connected with changes in conformation or chemical environment of the compound.

SS-NMR is also useful because it is able to determine the number of crystallographically inequivalent sites in a unit cell. Unlike PXRD, SS-NMR spectroscopy is well-suited to studying amorphous forms of pharmaceuticals and solvates that are usually small to detect. Collecting spectra at various temperatures is a powerful tool in understanding polymorphic transformations and molecular motion in the solid [178-180].

**Vibrational spectroscopy**
Most prominent among the vibrational spectroscopic methods for polymorph identification are infrared and raman spectroscopy. Both techniques offer information on structure and molecular conformation in the solid state by probing vibrations of atoms. These methods are especially important for characterization of polymorphs because hydrogen-bonding patterns often differ among forms and the functional groups affected will display shifts of varying degrees. Other information gained from vibrational spectroscopies, which can be helpful in distinction of polymorphs, includes low energy lattice vibrations caused by differences in crystal packing.

Infrared absorption spectroscopy has enjoyed the most use in polymorph investigations primarily because it is a robust technique available in most laboratories. Several limitations of the technique are worth considering especially for studies involving small quantities of sample or single crystals. These studies are most conveniently conducted by IR microscopy and this is the method of choice for studies on single crystals. However, an IR transparent substrate must be employed and it is difficult to collect spectra of all but the thinnest crystals due to transmittance issues. Substrate and sample transmittance issues can be circumvented by using attenuated total reflection (ATR) or diffuse-reflectance infrared (DRIFT) spectroscopy [181, 182].

Raman spectroscopy is a powerful light scattering technique used to diagnose the internal structure of molecules and crystals. In a light scattering experiment, light of a known frequency and polarization is scattered from a sample. A raman spectrometer interfaced to a microscope has an additional advantage of being able to pinpoint small crystalline samples, which do not have to be removed from crystallization vials for analysis, thus eliminating sample preparation. In addition, the spatial resolution of raman microscopy is limited by the wavelength of the visible light probe rather than infrared radiation, making this technique suitable for examining minute sample quantities in complex matrices. [183, 184]

**Water vapour sorption**
Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. The method requires accurate data of the hygroscopicity of both completely crystalline and completely amorphous samples. In some studies amorphous material were plasticized by water sorption and crystallized during the experiment. However crystallization can be accompanied by expel of water depending on the degree of hydration of crystalline material [185].

**Conclusion**
The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. Various techniques, described in this review, are successfully used for the preparation
of solid dispersion in the bench and lab scale and can be used at industrial scale also. With future development of this technology, solid dispersions will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

References


56. Reneker DH, Chun I. Nanometre diameter fibres of polymer, produced by


