SOLID DISPERSIONS: A REVIEW

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ABSTRACT
The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. Currently only 8% of the new drug molecules have high solubility and permeability. The solubility behaviour of a drug is key determinant to its oral bioavailability and it is the rate limiting step to absorption of drugs from the gastrointestinal tract. This results in important products not reaching the market or not achieving their full potential. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and bioavailability of a range of hydrophobic drugs. This article reviews the various preparation techniques for solid dispersion, types of solid dispersions based on molecular arrangement and other aspects such as selection of carriers and methods of characterization and their applications have been discussed.

KEYWORDS: Solid dispersion, solubility, selection of carriers

INTRODUCTION
In recent years due to application of combinatorial chemistry and high-throughput screening during drug discovery, a majority of new drug candidates have been discovered which exhibit poor aqueous solubility as these drugs are found to be very challenging for scientists in development of dosage forms. It is commonly recognized in the pharmaceutical industry that more than 40% of newly discovered drug candidates are poorly water soluble. The solubility behaviour of drugs remains one of the most challenging aspects in formulation development and also complicating the delivery of poorly water soluble drugs.1,2 Formulation challenges for poorly soluble compounds: 3

- Poor dissolution rate
- Low and variable bioavailability
- More potential for food effect
- Inability to deliver high doses for toxicology studies
- Difficulty in developing parenteral formulations

Many potential drug candidates are characterized by a low oral bioavailability. Often poor drug dissolution/solubility rather than limited permeation through the epithelia of the gastrointestinal tract are responsible for low oral bioavailability. Thus aqueous solubility of any therapeutically active substance is an important property as it governs dissolution, absorption and the invivo efficacy. Drugs with low aqueous solubility have low dissolution rates and thus suffer from low oral bioavailability problems.4 Poor solubility results in low bioavailability, increase in the dosage, large inters and intra-subject variation and large variations in blood drug concentrations under fed versus fasted conditions.5

A poorly water soluble drug has been defined in general terms to require time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract.6 Poorly soluble compounds as defined by the FDA Biopharmaceutical classification system:

Solubility in pH 1-8 solutions * 250 ml < Dose7

Factors causing poor solubility: 8

- High crystallinity/high MP
  - Zwitterion formation
  - Insoluble salts
  - H-bonding networks
- Hydrophobicity/High LogP
  - Lack of ionizable groups
- High molecular weight

To improve such poor solubility issues, solid dispersion techniques are widely applied to increase the solubility and enhance the oral bioavailability of poorly water soluble drugs. Therapeutic effectiveness of a drug depends upon the bioavailability and the solubility of drugs in oral formulations. But most of the time it becomes challenging to formulate poorly water soluble drugs. Various techniques are available to improve the solubility of drugs by various ways like salt formation, co-solvency, addition of solubilizing agent, micronization and complexation. But there are practical limitations with these techniques as the desired bioavailability enhancement may not always be achieved. One such approach that has been shown to properly enhance absorption of such drugs is to formulate and prepare solid dispersions.9

Formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs. Solid dispersion formulation was developed by Chiou and Riegelman. It has been used for a number of poorly soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid, carbamazepine, celecoxib and albendazole.5

SOLID DISPERSIONS

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method. The dispersion of drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersions may also be called solid-state dispersions.9

In this technique a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) products. Eutectic dispersions are homogeneous dispersions of crystalline or amorphous drugs in crystalline or amorphous carriers and in the solid solution the drug could be partially or completely soluble in the dispersing matrix. Presence of drug in microcrystalline state, improved wettability and formation of high free energy amorphous forms of the drug during solid dispersion formation contribute towards enhanced drug solubilisation.
MECHANISMS OF ENHANCED DISSOLUTION IN SOLID DISPERSIONS
The increase in dissolution rate for solid dispersions can be attributed to a number of factors. These include the following:

**Reduced Particle size or Reduced Agglomeration:** Both are related to increases in the exposed surface area of the drug. Size reduction has been considered to be a result of eutectic or solid solution formation. It has also been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. Many of the carriers used for solid dispersions may have some wetting properties hence it can be suggested that improved wetting may lead to reduced agglomeration and increase surface area.¹⁰

**Increased solubility or Dissolution Rate of the Drug:** Many of the carriers used may increase the solubility if the drug. There appear to be two sets of observations with regard to the mechanism of drug release from solid dispersions. In the first instance some systems appear to show carrier controlled release as the rate of release is controlled by the carrier and is independent of drug properties. Secondly some systems show release behaviour that is dependent on the properties of the drug rather the polymer.¹¹

**Transferring the drug from crystalline to Amorphous state/Formation of High Energy States:** Amorphous drugs represent the higher energy states and can be considered as cooled liquids. They have greater aqueous solubility than crystalline forms because the energy required to transfer a molecule from crystal is greater than required for non crystalline( amorphous) solid. For example the amorphous state of novobiocin is 10 times more soluble than crystalline form.¹²

**Wetting:** When a strong affinity exists between a liquid and solid, the liquid forms a film over the surface of the solid. When this affinity is non existent or weak the liquid has difficulty displacing the air and there exists an angle of contact between the liquid and the solid. This contact angle results from an equilibrium involving three interfacial tensions, those acting at the interfaces between the liquid and vapour phases, at the solid and liquid phases, and at the solid and vapour phases.¹³

**CLASSIFICATION OF SOLID DISPERSIONS**¹⁴
Based on the molecular arrangement of solid dispersion, the types of solid dispersions can be distinguished as follows:

**Categories of Solid Dispersions**
- Simple eutectic mixtures
- Solid solutions

**According to their miscibility**
- Continuous
- Discontinuous solid solutions

**According to the way in which the solvate molecules are distributed in the solvendum**
- Substitutional crystalline solid solutions
- Interstitial crystalline solid solutions
- Amorphous solid solutions
- Glass solutions
- Amorphous precipitation in a crystalline carrier

**IDEAL CANDIDATES FOR SOLID DISPERSION**

Many of the research that has been reported on solid dispersion technologies involves drugs that are poorly water soluble and highly permeable to biological membranes as with these drugs, dissolution is the rate limiting step to absorption. Hence the hypothesis has been that the rate of absorption invivo will be concurrently accelerated with an increase in the rate of drug dissolution. In the Biopharmaceutical Classification System (BCS) class II drugs are those with low aqueous solubility and high membrane permeability and therefore solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. According to the BCS, drug substances are classified in four groups as shown in table.¹⁵

**Biopharmaceutical Classification System (BCS).**

<table>
<thead>
<tr>
<th>Class</th>
<th>Permeability</th>
<th>Solubility</th>
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<td>Class I</td>
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<td>Class II</td>
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<td>Class III</td>
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<td>Class IV</td>
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**Selection of carriers:** 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 multi 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. The carriers to be used should have the following characteristics:
- Readily soluble in water and in gastrointestinal fluids
- Physiologically inert
- Melting point not much higher than that of drug
- Thermal stability at melting temperature
- Low vapour pressure
- High molecular weight
- They should be non toxic
Polyethylene glycol 20000 (PEG 20,000), PEG 6000, PEG 4000, urea, PVP, desoxycholic acid, citric acid, pentaerythritol etc. are some of the carriers which have been generally used.¹⁶

**ADVANTAGES OF SOLID DISPERSIONS**

- **Particles with reduced particle size and increased dissolution rate:** 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. Due to this a high surface area is formed resulting in an increased dissolution rate and improved bioavailability.¹⁷

- **Particles with improved wettability:** A strong contribution to the enhancement of solubility is related to the drug wettability improvement 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 increase the wettability property of drug. Carriers can also influence the drug dissolution profile by direct dissolution.¹⁸

- **Particles with higher porosity:** Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity depends on the carrier properties, for instance solid dispersions containing linear polymers produce larger and more porous particles.
than those containing reticular polymers and so result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.\(^\text{29}\)

- **Drugs in amorphous state:** Poorly water 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 proposed that, if drugs precipitate it is as a metastable polymorphic form with higher solubility than the most stable crystal form.\(^\text{20}\)

**DISADVANTAGES OF SOLID DISPERSIONS**

- Poor stability is a major disadvantage of solid dispersion. The amorphous state of a drug may undergo crystallization.\(^\text{21}\)
- Ageing may decrease the dissolution rate and there may be changes in crystallinity.
- Due to tackiness in some solid dispersions, it sometimes leads to handling problem.
- Solid dispersions may be deteriorated in presence of moisture and excessive temperature. The presence of moisture influences the crystallinity of drugs.\(^\text{22}\)
- Some polymers used in solid dispersion are hygroscopic in nature and may adsorb moisture, that can result in crystal growth or the amorphous form may get converted to crystalline state.
- Some times the metastable form of a drug may change to stable form. So there may be decrease in solubility and dissolution rate.

**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.\(^\text{23}\) 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 Reigelman. To facilitate faster solidification, the homogeneous melt was poured in the form of a thin layer onto a ferrite plate and cooled by flowing air or water on the opposite sides of the plate. The solidified masses of drug-polyethylene glycol polymer systems were often found to require storage of one or more days in a dessicator at ambient temperatures for hardening and ease of powdering.\(^\text{24}\) The advantages of direct melting method are its simplicity and economy. The disadvantage is that many substances either drugs or carriers may decompose or evaporate during the fusion process at high temperatures.

- **Solvent method:** This method has been used for a long time in the preparation of solid solutions or mixed crystals of organic or inorganic compounds. They are prepared by dissolving a physical mixture of two solid components in a common solvent followed by evaporation of the solvent. This method was used to prepare solid dispersions of griseofulvin-polyvinylpyrrolidine, sulfathiazole-polyvinylpyrrolidine, steroid-polyvinylpyrrolidine and reserpine-deoxycholic acid. The main advantage of solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. The disadvantage of this method is the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of the negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent and the difficulty of reproducing crystal forms.\(^\text{25}\)

- **Melting-Solvent method:** It was shown recently that 5-10% (w/w) of liquid compounds could be incorporated into PEG 6000 without significant loss of its solid property. So it is possible to prepare solid dispersions by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol obtainable below 70\(^\circ\)C without removing the liquid solvent. The polymorphic form of the drug precipitated in the solid dispersion may be affected by the liquid solvent used. Such a method possesses both the advantages of the melting and solvent methods. But it is only limited to drugs with a low therapeutic dose. The feasibility of this method was demonstrated on spironolactone-polyethylene glycol 6000 and griseofulvin-PEG 6000 systems.\(^\text{26}\)

- **Melt agglomeration process:** This technique has been used to prepare solid dispersion where the binder acts as a carrier. Binder (carrier), drug and excipients are heated to temperature above the melting point of the binder (melt-in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer.\(^\text{27}\) The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and a higher binder content can be incorporated in the agglomerates. Larger particles result in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

- **Spray drying:** It is a method which is initiated by atomizing suspensions or solutions into fine droplets followed by a drying process, resulting in solid particles. 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.\(^\text{28}\) Rankell et al. prepared solid dispersions of loperamide with PEG 6000 by this technique wherein solutions containing different concentrations of PEG 6000 and constant amount of loperamide were spray dried. After spray drying, the dispersions were dried at 40\(\circ\)C under vaccum until constant weight. Solvent used was dichloromethane. The prepared solid dispersions exhibited higher dissolution rates than that of pure crystalline loperamide. The spray drying technique is a useful method to obtain spherical particle and narrow distribution.\(^\text{29}\)

- **The use of surfactant:** Surfactant reduces hydrophobicity of drug by reducing interfacial or surface
tension and because of this unique property surfactants have attracted the attention of investigators for preparation of solid dispersions. Recently a new class of surfactant known as Gelucires are introduced which identify by melting points and HLB values. Gelucire is widely used in the formulation of solid dispersions. Gelucires with low HLB can be employed to decrease the dissolution rate of drugs and higher HLB ones for fast release. Solid dispersions of antiviral agent uc-781-PEG 6000-gelucire 44/14 and UC-781-PEG 6000-gelucire 44/14-PVP k30 were studied. Improvement in solubility, dissolution and stability was observed. The amphoteric poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPO-PEO) block polymers, known as poloxamer represent another class of surfactants. These are available in various molecular weights and PEO/PPO ratios and offer a large variety of physicochemical properties. Polysorbate 80 a surfactant results in improvement of dissolution and bioavailability of poorly water soluble drug attributed to the solubilisation effect of surface active agent. It also ensures complete release of drug in metastable finely dispersed state having large surface area.

Labrasol, of same chemical nature as gelucire, is a clear liquid surfactant with a HLB of 14. Solid dispersions of piroxicam with labrasol have also resulted in improved solubility and dissolution when compared with pure drug. Inutec SPI, a derivative of insulin prepared by the reaction between isocyanates and the polycrylactone backbone has also been evaluated as carrier in formulation of solid dispersions for a poorly water soluble drug. Dissolution properties of SD(s) made up of itraconazole and Inutec SPI were improved in comparison to pure itraconazole or physical mixtures with Inutec SPI.

Alternative strategies for preparation of solid dispersions.

- **Spraying on sugar beads using a fluidized bed coating system:** The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce granules ready for tabletting or drug coated pellets for encapsulation in one step. The method has been applied for both controlled and immediate release solid dispersions.

- **Itraconazole** (Sporanox oral capsules, Janssen Pharmaceutica, Titusville, NJ) coated on sugar sphere, is made by layering onto sugar beads a solution of drug and hydroxypropylmethylcellulose (HPMC) in an organic solvent of dichloromethane and ethanol. A solid solution of drug in HPMC is produced upon coating (cosolvent evaporation) and controlled drying of coated beads in a closed Wurster process. As this thin film dissolves in water or gastric fluid, the molecularly dispersed itraconazole is released at supersaturated concentration. HPMC acts as a stabilizer to inhibit recrystallization of the itraconazole. The supersaturated solutions of itraconazole are sufficiently stable to allow for absorption and distribution.

- **Hot melt extrusion:** Many studies have been conducted on this process for the preparation of solid dispersion. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component results to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step. Hot-melt extrusion method is used in the preparation of various dosage forms in the pharmaceutical industry such as preparation of sustained-release pellets. The advantages of hot-melt extrusion include lower temperature and shorter residence time of the drug carrier mix (<2 minutes), absence of organic solvents, continuous operation possibility, minimum product wastage, good control of operating parameters, and possibility to scale up. The disadvantages are few and mainly relate to negative effects of shear force.

A fast-release dosage form of carbamazepine was prepared using lactose as a hydrophilic filler and PEG 4000 as a binder at a temperature below its melting point. Solubility and the dissolution rates of 17 β-estradiol hemihydrate was improved using PEG 6000, polyvinylpyrrolidone (PVP), or Gelucire 44/14 employing this process. Solid dispersions prepared by hot-melt extrusion have been used for clinical testing.

- **Direct capsule filling:** The filling of semisolids into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978. Laboratory-scale semiautomatic equipment and large-scale manufacturing equipment for direct capsule filling are commercially available. 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). This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing crosscontamination 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. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (eg, polysorbate 80 with PEG, phosphatidylethanolamine with PEG). The temperature of the molten solution should not exceed ~70-C because it might compromise the hard-gelatin capsule shell.

- **Electrostatic spinning method:** The electrostatic spinning method technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology. This technology is now applied in the pharmaceutical field. 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. 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 using this technique. Because the technique has been successfully used in other fields, the technique can be extended in the pharmaceutical industry for the preparation of solid dispersions.

- **Surface active carriers:** A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs. In addition to their use as excipients to improve the physical and chemical characteristics of the formulation, surface active carriers may be included to improve the efficacy of the product. The properties of surfactant are such that they can alter the thermodynamic activity, solubility, diffusion, disintegration and dissolution rate of a drug. Each of these parameters influences the rate and extent of drug absorption. Surface active carriers can exert direct effects on biological membranes thus altering drug transport across the membrane. The surface-active and self-emulsifying carriers for solid dispersion of poorly watersoluble drugs have been of great interest in recent years. Two of the important surface-active carriers are Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Gelucire 44/14 has commonly been used in solid dispersion for the bioavailability enhancement of drugs. Gelucire 44/14 is a mixture of glyceryl and PEG 1500 esters of long-chain fatty acids and is official in the European Pharmacopoeia as lauryl macrogolglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic-lipophilic balance (HLB) value.

A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-active carrier. 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. These PEG-polysorbate carriers have been found to enhance dissolution and bioavailability of drugs from the solid dispersions. Incorporation of 5% (wt/wt) phosphatidylcholine resulted in enhanced dissolution rate of nifedipine from a PEG-based solid dispersion. Pulverized solid dispersions in PEG containing varying amounts of ionic and nonionic surfactants, including sodium dodecyl sulfate and Polysorbate 80 gave increased dissolution rate of drug.

One of the limitations of bioavailability enhancement by this method might be the low solubility of drug in available carriers. The desired doses of a drug cannot be solubilized and filled into hard-gelatin capsules if adequate solubility in a carrier cannot be obtained.

- **Supercritical fluid technology:** It has been known 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. In the pharmaceutical field, the SCF technology was industrially applied in the early 1980s; the applications included the purification of surfactants and pharmaceuticals, fractionation of polymeric materials and chemical reactions and polymerizations. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc).

A solid dispersion of Carbamazepine in PEG-4000 increased the rate and extent of dissolution of carbamazepine. In this method a precipitation vessel was loaded with solution of Carbamazepine and PEG-4000 in acetone, which was expanded with supercritical CO2 from the bottom of the vessel to obtain solvent free particles. The physical and thermal properties of SCFs fall between those of the pure liquid and gas. SCFs offer liquid like densities, gas like viscosities, gas like compressibility properties and higher diffusivities than liquids. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propane, ethanol and water. Of these CO2 is a widely used SCF in the pharmaceutical processing due to its low critical temperature and pressure which make it attractive for processing heat-labile molecules.

SCF technology provides a novel alternative method of generating small particles, with higher surface areas that are free flowing and very low in residual organic solvent. These aspects of the technology can be applied to formulate coprecipitates of drug in water-soluble carrier and overcome many problems of conventional methods. The solid dispersion prepared from this method has been found to increase the dissolution considerably. This technique has also been used to precipitate homogeneous antracene-phenantrene crystals of solid solution.

**CHARACTERIZATION OF SOLID DISPERSION**

A. Detection of crystallinity in solid dispersions: Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Many attempts have been made to investigate the molecular arrangement in solid dispersions. Many techniques are available which detect the amount of crystalline material in the dispersion.

Currently, the following techniques are available to detect the crystallinity:

- **Powder X-ray diffraction:** It can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material.
- **Infrared spectroscopy (IR):** It can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy was used to accurately detect crystallinities ranging from 1 to 99% in pure material.
- **Isothermal Microcalorimetry:** It measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg).
- **Dissolution Calorimetry:** It measures the energy of dissolution, which is dependent on the crystallinity of the sample, usually dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.
- **Macroscopic techniques** can be indicative for the degree of crystallinity. Density measurements and...
Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity.

- **A technique used to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC).** In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Also the melting and crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

**B. Detection of molecular structure in amorphous solid dispersions**
The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The following techniques are used:

- **Confocal Raman Spectroscopy** was used to measure the homogeneity of the solid mixture of ibuprofen in PVP. It was described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution.

- **Using IR or FTIR,** the extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters.

- **Temperature Modulated Differential Scanning Calorimetry (TMDCS)** can be used to assess the degree of mixing of an incorporated drug. Due to the modulation reversible and irreversible events can be separated. This technique can be used to assess the amount of molecularly dispersed drug and from that the fraction of drug that is dispersed as separate molecules is calculated.

**STUDIES ON SOLID DISPERSION**
Solid dispersion of aceclofenac was prepared using Avicel 200 and Sylsia 350 as polymers in different ratios. It was prepared by using kneading method. In the studies it was found that there was low in vitro dissolution rate of pure aceclofenac as compared to dissolution rate of aceclofenac from solid dispersion which was significantly higher. It was found that there was high dissolution rate of Avicel 200-aceclofenac solid dispersion as compared to that of Sylsia 350-aceclofenac solid dispersion. It was concluded that solid dispersion technique can be used to improve the dissolution profile of aceclofenac.

The influence of hygrosopicity of polymers on phase behaviour of amorphous solid dispersions in the presence of moisture was studied. In the studies before and after exposure to high relative humidity drug-polymer miscibility were measured using Infrared spectroscopy and differential scanning calorimetry. Polyvinylpyrrolidone, hypromellose acetate succinate were chosen as polymers. The drugs such as indomethacin, felodipine, pimozide and quinidine were selected. After investigation it was proposed that a less hygroscopic polymer with strong drug-polymer interactions will be less prone to moisture induced phase separation.

Risperidone loaded solid dispersion were prepared using methyl-a-cyclodextrin as a carrier by using solvent evaporation method. For a faster release of drug solid dispersion of drug was incorporated into orally disintegrating tablets. D-mannitol or galenIQ53-721 as diluent and Kollidon or sodium starch glycolate as superdisintegrant were used in preparation of tablets. It was observed that formulation containing galenIQ53-721 and sodium starch glycolate show increased disintegration time whereas this time decreased for formulation containing mannitol and Kollidon.

Solid dispersions of indomethacin were prepared and characterized. Solid dispersion of drug with carrier Gelucire 50/13 and polyethylene glycol 4000 was prepared by using hot melting method. The physical state of the drug was examined through scanning electron microscopy, differential scanning calorimetry and X-ray powder diffraction. It was found that there were 4-folds enhancement in drug solubility.

The effect of different types of polymer on the dissolution rate of amorphous felodipine solid dispersions was studied. Poly(vinylpyrrolidone) and hydroxypropyl methylcellulose acetate succinate were chosen as polymers. It was founded that hydroxypropyl methylcellulose acetate succinate maintain the high level of supersaturation for longer time which resulted in increased dissolution rate of the amorphous solid dispersions.

Griseofulvin-loaded solid dispersion were prepared and dissolution profile of griseofulvin was evaluated from griseofulvin-succinic acid eutectic mixture. Studies were done on factors which enhance the dissolution rate of griseofulvin from its dispersion in succinic acid. It was found that dissolution rates of griseofulvin from solid dispersions was influenced by particle size of drug in solid dispersions of griseofulvin.

**APPLICATIONS OF SOLID DISPERSION**
- Increases oral bioavailability of poorly water soluble drugs.
- Solid state suitable for oral delivery.
- No change in chemical properties of the drug.
- Relatively simple processing techniques.
- Increases dissolution due to metastable solid state.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained release dosage form.
- To formulate sustained release regimen of soluble drugs by using insoluble carriers.
- To reduce presystemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into isomorphous, solid solution, or eutectic compounds.

**FUTURE PROSPECTS OF SOLID DISPERSIONS**
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. Because of the simplicity of manufacturing and scaleup processes the physicochemical properties and the bioavailability are not expected to change during the scale up. Due to this the popularity of solid dispersions to solve bioavailability issues with respect to poorly water soluble drugs will grow rapidly. One major area of research will be
the identification of new surface-active and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are available for oral use. One limitation in the development of solid dispersion may be the inadequate drug solubility in carriers, so there has to be a wider choice of carriers. There should also be research for identification of excipients that can prevent crystallization of drugs from supersaturated systems. Physical and chemical stability of both the drug and carrier in a solid dispersion are major issues, so research also needs to be done towards stability issues. 

**CONCLUSION**

Solubility is an important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of a drug is the rate determining step for oral absorption of the poorly water soluble drugs which can affect the in vivo absorption of drugs. Because of solubility problem of many drugs the bioavailability gets affected and so solubility enhancement becomes necessary. Solid dispersion technology is one of the possible methods that increase the solubility of poorly soluble drugs. The various technologies discussed have been successful in the laboratory as well as the scale-up.

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