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SOLID DISPERSION: STRATEGIES TO ENHANCE SOLUBILITY AND DISSOLUTION RATE OF POORLY WATER-SOLUBLE DRUG

N. M. Hande

Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Sec-08, CBD Belapur, Navi Mumbai - 400614, Maharashtra, India.

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Correspondence to Author:
N. M. Hande

Assistant Professor,
Department of Pharmaceutics,
Bharati Vidyapeeth College of Pharmacy, Sec-08, CBD Belapur,
Navi Mumbai - 400614, Maharashtra, India.

E-mail: nileshhandesalse@gmail.com

ABSTRACT: The solubility problem of drugs is always one of the most challenging aspects in formulation and development of dosage forms. In fact, most of new chemical entities are poorly water soluble and not well-absorbed after oral administration resulting in low bioavailability. The current challenges of the pharmaceutical industries are related to techniques that improve the water solubility of drugs. Solid dispersions are one of the most successful strategies to enhance the oral bioavailability of poorly water-soluble drugs by reducing particle size and improving drug wettability. This article reviews various types of solid dispersion, and their preparation techniques. Some of the practical aspects to be considered for the preparation of solid dispersions are selection of carrier and methods of physicochemical characterization thorough study of nature of drug in solid dispersion etc. are discussed. At the end of the article commercialization of some solid dispersion and recent revival has been considered. This article gives scope for research in enhancement of solubility of poorly water-soluble drugs.

INTRODUCTION: The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bioavailability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in poor wettability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have reduced the incidence of these problems and enhanced dissolution.

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The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by co-solvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles.

The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. Solid

dispersion technique was firstly demonstrated by Sekiguchi and Obi. They proposed the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carries like urea. Upon exposure to aqueous fluids the active drug released into fluids is fine, dispersed particles because of fine dispersion of the drug in the solid eutectic mixture and the faster dissolution of the soluble matrix. The eutectic mixture contained 52 per cent w/w of sulfathiazole and 48 per cent w/w of urea.

Solid Dispersion: Chiou and Riegelman 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" [11]. The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Sekiguchi *et. al.* Suggested that the drug was present in a eutectic mixture in a microcrystalline state, after few years Goldberg *et. al.* Reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution. Once the solid dispersion was exposed to aqueous media & the carrier/es dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly Water soluble drugs were expected to be high.

The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems which may be overcome by using surface active and Self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. 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. Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion), solvent or melting solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersion, a first stated by Mayersohnand Gibaldi.

Merits of Solid Dispersions:

- Improved wettability results in increase solubility.
- Particles having higher porosity Increase in porosity influence carrier properties and increase drug release profile.
- Amorphous state of drug leads to enhancement in drug release.
- Pre-systemic metabolism is reduced due to increase in dissolution rate and absorption.
- Liquid form of drug can be transferred in solid form.
- Solid dispersions technique is prominent over other techniques such as particle size reduction.
- Particle size reduction in solid dispersion leads to increase surface area which cause increase in dissolution rate hence bioavailability is improved.
- By changing water solubility drug bioavailability can be increased [13].

Demerits of Solid Dispersions [12, 14, 15]:

- Instability of solid dispersions.
- Physical properties of solid dispersions are affected by moisture and temperature.
- Tackiness property of solid dispersions makes it difficult to handle.
- Difficult to prepare solid dispersions in a dosage form.
- Stability problem of vehicle and drug.
- Physicochemical properties reproducibility**.**
- To achieve good dissolution large amount of carrier is required.

Ideal Candidates for Solid Dispersion: Much 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 the dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption *in-vivo* will be concurrently accelerated with an increase in the rate of drug dissolution. 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 1** (FDA 2000).

Table 2 represents some BCS Class II drugs on the WHO model list of Essential Medicines. The table is adopted from Lindenberg, 2004, only for the BCS Class II drugs.

TABLE 1: BIOLOGICAL CLASSIFICATION SYSTEM

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

TABLE 2: SOME BCS CLASS II DRUGS ON THE WHO MODEL LIST OF (BCS) ESSENTIAL MEDICINES

Drug	Used as
Carbamazepine	Antiepileptic
Dapsone	Antirheumatic/leprosy
Griseofulvin	Antifungal
Ibuprofen	Pain relief
Nifedipine	Ca-channel blocker
Nitrofurantoin	Antibacterial
Phenytoin	Antiepileptic
Sulfamethoxazole	Antibiotic
Trimethoprim	Antibiotic
Valproic acid	Antiepileptic

Type of Solid Dispersion: The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Therefore, based on their molecular arrangement, four different types of solid dispersions can be distinguished. They are described below.

1. Eutectics

2. Amorphous precipitations in crystalline matrix

3. Solid solutions

a. Continuous solid solutions

b. Discontinuous solid solutions c. Substitution solid solutions d. interstitial solid solutions

4. Glass suspensions and solutions [18]

Eutectics: Eutectics are prepared by rapid solidification process. In this process two components form fused melt which are crystalline in nature. Where they are completely miscible in liquid state but very less miscible in solid state [19].

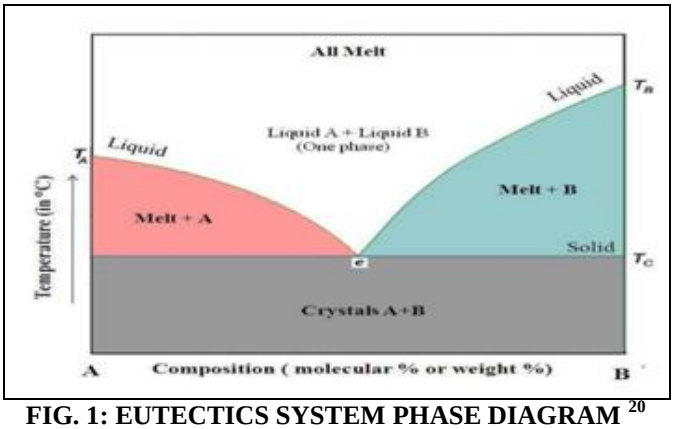

FIG. 1: EUTECTICS SYSTEM PHASE DIAGRAM [20]

Amorphous Precipitation in Crystalline Matrix: In this within the amorphous solvent the solute molecules are dispersed irregularly and molecularly. In earlier studies other carriers were used such as urea and sugars (sucrose, galactose and dextrose). But now a day's cellulose derivatives and organic polymers are used (PVP, PEG *etc*). To plasticize the polymer various solute molecules are used. The reduction in glass transition temperature is due to solutes which are used to plasticize the polymer [21].

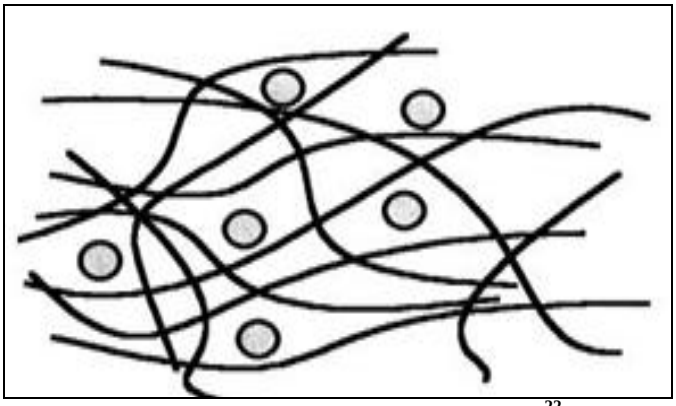

FIG. 2: AMORPHOUS SOLUTIONS [22]

Solid Solutions: Solid solution dissolution depends on the dissolution rate of matrix. Solid solutions are just like liquid solutions but in this only one phase exists but number of components can vary. In this in a solid solvent solid solute is dispersed. Drug particle size is also reduced [23]. They are further classified according to their miscibility and other in which the solute molecules are dispersed in solvendum [24].

According to Miscibility:

Continuous Solid Solutions: In this type the components are miscible in all proportions. This means bonding strength between two, components is more than the bonding strength between individual components. These types of solutions are not yet prepared [19]. Due to heteromolecular bonding strength is more than monomolecular in which continuous solid solution form because of these continuous solid solutions lattice energy is more than the pure components in solid state [24].

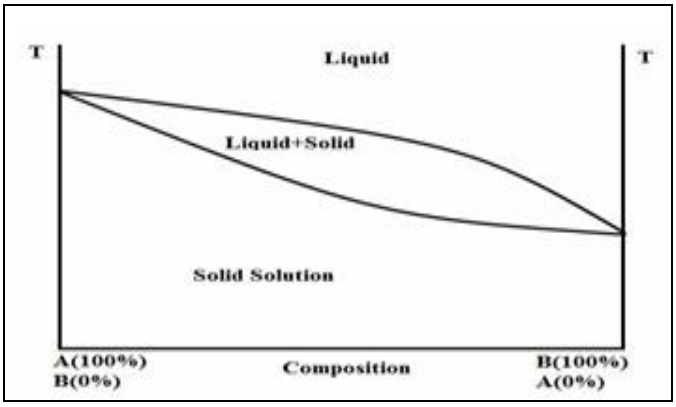

FIG. 3: CONTINUOUS SOLID SOLUTION PHASE DIAGRAM [25]

Discontinuous Solid Solutions: In this type solubility of one component in other type is very less or it is partially miscible.

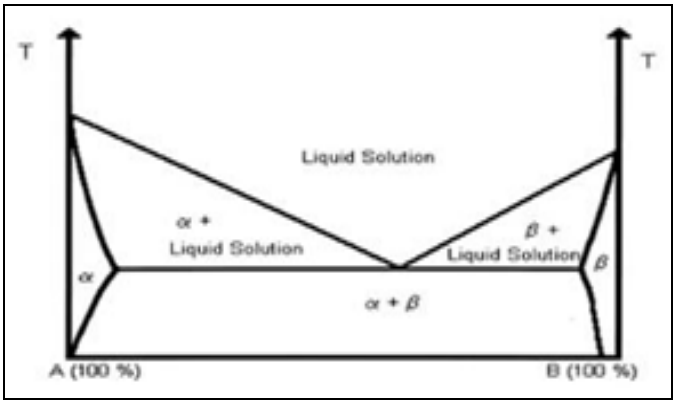

FIG. 4: DISCONTINUOUS SOLID SOLUTIONS PHASE DIAGRAM [19]

According to Solute Molecule are dispersed in Solvendum:

Substitutional Solid Solutions: In this solvent molecules in the crystal lattice of the solid solvent are substitute by the solid molecules in substitutional solid solutions.

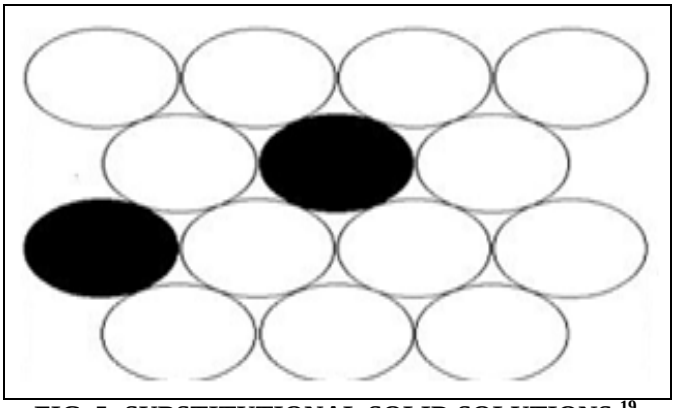

FIG. 5: SUBSTITUTIONAL SOLID SOLUTIONS [19]

Interstitial Solid Solutions: In this between the solvent molecules in the crystal lattice the dissolved molecules occupy the interstitial spaces. The molecular diameter of the solute molecules in case of interstitial solid solutions should not be greater than solvent molecules diameter i.e. 0.59 and solvent molecules have more than 20% diameter than solute molecules [17].

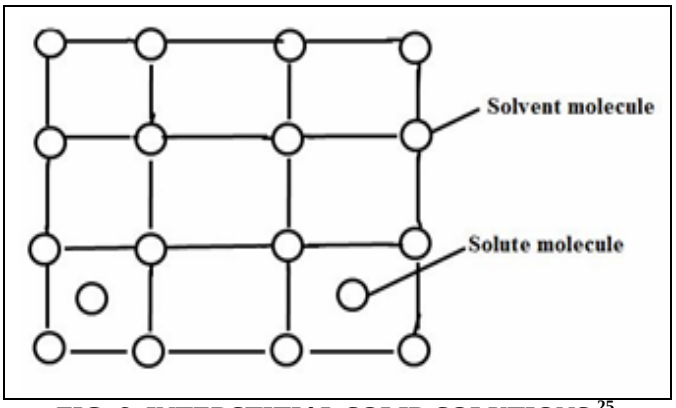

FIG. 6: INTERSTITIAL SOLID SOLUTIONS [25]

Glass Suspensions and Solutions: Glass suspension is a mixture where glassy solvent contains suspended precipitated particles. And Glass solutions represent homogenous system in which glassy solvent contains dissolved solute [16]. Glass means a glassy or vitreous state containing either mixture of chemicals or pure chemicals. Below the glass transition temperature, the glassy state is characterized by transparency and brittleness [17].

By an abrupt quenching of the melt glassy or vitreous state are formed. Many compounds like glucose, sucrose, citric acid, PVP, and ethanol etc. form glasses when their liquid state is cooled. Linear and flexible chain polymers show glassy state of transparency and brittleness as the freeze [16].

Method of Preparation of Solid dispersion [61, 62]:

- Solvent method
- Fusion method
- Spraying on Sugar Beads using Fluidized Bed Coating
- Melting solvent method
- Melt agglomeration method
- Solvent evaporation method
- Gel entrapment technique
- Kneading method
- Co-grinding method
- Use of surfactant
- Supercritical fluid method
- Freeze drying (Lyophilization method)
- Extruding method
- Spray drying
- Electro spinning
- Effervescent method
- Direct capsule filling
- Co-precipitation method
- Surface active carrier
- Dropping method

Solvent Method:

Step 1: Drug and matrix material solution is prepared.

Step 2: Solvent is removed forming solid dispersion.

Advantages: As evaporation of organic solvent is carried at low temperature so thermal degradation of drug and carrier can be prevented.

Disadvantages:

1. Chemical stability of drug.
2. Incomplete removal of liquid organic solvent.
3. Costly method of preparation [60].

Fusion Method:

Step 1: Physical mixture of drug and carrier are heated and melted.

Step 2: Cool and solidify the melted mixture rapidly in an ice bath with continuous stirring.

Step 3: Solid mass formed then crushed and sieved. For hardening and ease of powdering the solidified mass formed is stored for 1 or more days in desiccator at ambient temperature [14].

Advantages:

1. To prevent oxidation of drug and carrier inert gas such as nitrogen can be used.
2. Simple and economic method.

Disadvantages:

- ❖ Incompatibility of drug and carrier.
- ❖ Miscibility between drug and carrier changes when it is cooled.
- ❖ Due to heating at high temperature degradation of drug and carrier can occur.
- ❖ Sometime phase separation can occur [60].

Hot Melt Extrusion Method: In this drug is embedded in polymer during shaping to form product. This extruder is required for mixing of components [14].

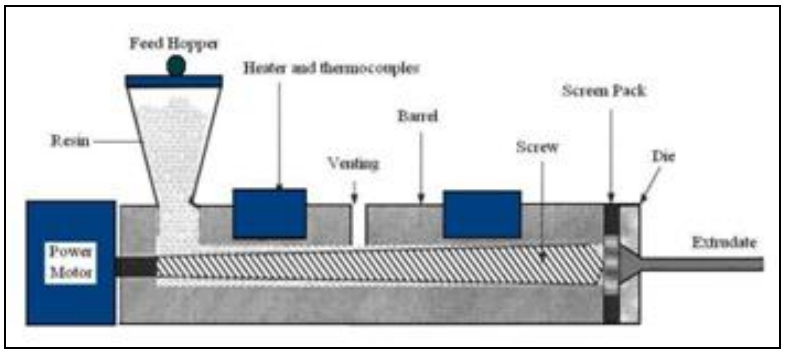

FIG. 7: SCHEMATIC SHOWING COMPONENTS OF A SINGLE SCREW MELT EXTRUDER [20]

Advantages:

1. Continuous production can be achieved through this process.

2. This does not require solvent [63].

Supercritical Fluid Method: Supercritical fluid technology is important because it operates at high temperature and pressure. Above critical temperature and pressure supercritical fluid exists as single phase. The most used SCF is CO2 due to its low temperature (31.3 degree C) and low pressure (73.8 bar). It is used because it nontoxic, non-inflammable, inexpensive and for processing heat labile molecules. In this drug and inert carrier are dissolved in carbon dioxide solvent and are sprayed by nozzle with low pressure on expansion vessel and particles are formed. And then the expansion of mixture is rapidly cooled. Another name of this technique is rapid expansion of supercritical solution (RESS) [64].

Spray Drying: In spray drying method drug and polymer are suspended or dissolved in a solvent or solvent mixture. To remove the solvent mixture is then dried in stream of air which is heated. Due to spray drying drug which is obtained is in amorphous form and can also be in crystalline form [65].

Melt Agglomeration Method: In this technique carrier is used which act as a binder. Prepared by heating binder by heating drug and excipient above melting temperature or using high shear mixture heating excipient in a molten binder in which drug dispersion is sprayed. Its critical parameters are: Particle size, manufacturing method and types of binder [18].

Kneading Method: Drug and carrier mixture is prepared in a mortar which is then moisten in methanol. This mass is then kneaded for 30 minutes and for 24 hours it is then dried under vacuum. It then passed through sieve.no.60 to produce fine powder and finally stored in desiccator [66].

Effervescent Method: In this sodium bicarbonate and organic acids (tartaric, succinic and citric acid) are incorporate in effervescent solid dispersions. The combination of organic acids in poorly water-soluble drugs yield effervescent solid dispersions which leads to increase dissolution and absorption of poorly water soluble drugs [20].

Lyophilization Technique (Freeze drying): In a common solvent the carrier and drug are co dissolved, then frozen which are then lyophilized in which molecular dispersion is formed. So, it is a type of molecular mixing technique [12, 67].

Electro Spinning: A drug polymer liquid stream is subjected to potential between 5 and 30 kV. At interface the surface tension of drug / polymer solution is overcome by electrical forces. Then submicron diameter fibers are formed. The fibers are then collected on screen as the solvent evaporates which gives non-woven fabric. The formed fibers diameter depends upon feeding rate, dielectric constant, surface tension, and electric field strength [68].

Direct Capsule Filling: In this technique large scale manufacturing equipment and laboratory scale semiautomatic equipment is used. Liquid melt of solid dispersion is directly filled in to hard gelatin capsule due to this it overcomes the problem due to grinding which cause change in crystalline behavior of drug. Example Molten dispersion of triamterene-PEG 1500 can be filled in hard gelatin capsule using Zanasi LZ 64 capsule filling machine [61].

Surface Active Carrier: In solid dispersion the drug can be dispersed in a carrier molecularly to form a solution / it can either be dispersed in particle form. Drug can be partially dissolved/ dispersed in a carrier. But in certain cases, drug in the form of particulates is dispersed but is dissolved to a very less extent in vehicle. Due to this reason in case of solid dispersion of poorly water-soluble drugs a surface-active carrier is preferred [26].

Use of Surfactant: To increase solubility surfactants are used. Surfactant work by reducing surface tension and interfacial tension which causes reduction in hydrophobicity of drug. Due to this property surfactants are used in solid dispersions [69]. Gelucires a new class of surfactant which is used to prepare semi solid dispersions are mainly identified by HLB values and melting point.

Gelucires are amphiphilic and solid waxy materials. Surfactant has a unique property of plasticization and solubilization which causes reduction in melting of active pharmaceutical ingredient [70].

Melting Solvent Method: It is combination of two methods *i.e.* fusion method and solvent method. In this in a suitable solvent drug is dissolved then mixing with molten carrier occurs which is then cooled and solidified. As it uses less temperature it offers advantage for thermolabile drugs [67].

Properties of Carrier used for Solid dispersions [20, 71]:

- Should be pharmacologically inert and nontoxic.
- Should be water soluble with enhancing dissolution properties.
- Solubility in large amount of solvents.
- Should be compatible with drug.
- Should increase the aqueous solubility of drug.
- Due to low melting point of melt method they are heat stable.
- Should form only weak bound complex.
- Should have good flow index and compressibility index.
- Glass transition point should be high and with Improve stability.
- Should form solid solution in presence of drug.
- Should have property of protecting drug from moisture.

Selection of Solvents [72]: Solvent to be included for the formulation of solid dispersion should have the following criteria:

1. Both drug and carrier must be dissolved.
2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
3. Ethanol can be used as alternative as it is less toxic.
4. Water based systems are preferred.
5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken into consideration.

TABLE 3: AN OVERVIEW OF COMMON ORGANIC SOLVENTS [72]:

Solvent	Melting point (°C)	Boiling point (°C)	Vapour pressure at 25°C (kPa)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Chloroform	-63	62	26.1
DMSO	19	189	0.08
Acetic acid	17	118	1.64

Table 4: VARIOUS CARRIERS USED IN SOLID DISPERSION ALONG WITH ITS CHARACTERISTICS [73]

Carrier	Characteristic
PEG (Polyethylene glycol	Polyethylene glycols (PEGs) are polymers of ethylene oxide. Molecular weight (MW) in the range 200 ± 3, 00,000. Good solubility in water but decreases with molecular weight. In manufacture of solid dispersions PEGs of MW 4000-6000 are the most used. Various drugs with increase release rate using PEG 6000 are ofloxacin, silymerin, gliclazide ,dapsone, mebendazole, Cisapride, Nitrendipine, oxazepam, valdecoxib , isosorbide dinitrate, zolpidem, piroxicam, fenofibrate, glibenclamide, ketoprofen
PVP (Poly-vinyl pyrrolidone)	Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) Molecular weight: 2500 to 3,000,000 According to K Value they are classified. Improve wettability of dispersed compound and have increase water solubility. Various drugs with increase release rate are diflunisal, nifedipine, tanshinone, cefuroxime axetil, flunarizine, daidzein, nitrendipine, ketoprofen, bicalutamide, quercetin, lansoprazole.
Sugars	Lactose is used as a carrier for production of solid dispersion with drugs containing primary amide group

	□ Chitosan, a derivative of the polysaccharide chitin whi formed by deacetylation at the N position, used as a carrier in solid dispersions. □ Mannitol can also be used to prepare solid dispersions □ Various drugs with increase solubility using sorbitol are □nitrofurantoin, prednisolone, ofloxacin and ursodeoxycholic acid.
Urea	□ Urea is the end product of human protein metabolism Light diuretic effect. □ Non-toxic. □ Solubility is greater than 1 and also exhibit good solubility in many organic compounds. □ Increase dissolution rate of chloramphenicol and piroxicam.
Emulsifiers	□ Emulsifying agent also improve the release behavior of many drugs. □ Two mechanisms: Improvement of wetting characteristics and solubilization of the drug. □ Due to toxicity problem they are used in combination. □ Mixture of PEG 6000+ Tween 20 enhanced release rate of mefenamic acid. □ PEG 4000+SLS increase solubility of fenofibrate solid dispersion. □ PEG 6000+ Polysorbate 80 increase solubility of nitrendipine solid dispersion by 7 fold.
Polyacrylates And Polymethacrylates	□ Polyacrylates and polymethacrylates are glassy substances. □ Produced by polymerization of acrylic and meth acrylic acid, and their derivatives such as esters amides and nitriles. □ They are mainly used as coating to modify the release of drugs. □ They are mainly Eudragits. □ Eudragits E is used to increase the release rate.
Cellulose derivative	□Celluloses are naturally occurring polysaccharides in the plant kingdom. □ High molecular weight unbranched substances. □ In this saccharide units are linked by β-1, 4-glycoside bonds. □ Various cellulose derivatives are methyl cellulose, hydroxyl propyl cellulose, hydroxy propyl methyl cellulose. □HPMC solid dispersion with increase dissolution rate are paracetamol.
Miscellaneous	□Dicalcium phosphate, silica gel sodium chloride, skimmed milk, microcrystalline cellulose etc.

Characterization of Solid Dispersion: Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions.

However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion [72].

Drug -carrier Miscibility:

- Hot stage microscopy
- Differential scanning calorimetry
- Powder X-ray diffraction
- NMR 1H Spin lattice relaxation time

Drug Carrier Interactions:

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

Physical Structure:

- Scanning electron microscopy
- Surface area analysis
- Surface properties
- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

Amorphous Content:

- Polarized light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- ITC
- Powder X-ray diffraction

Stability:

- Humidity studies
- Isothermal Calorimetry
- DSC (Tg, Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

Dissolution enhancement

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media

Powder X-ray Diffraction: Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material.

Infrared Spectroscopy (IR): Infrared spectroscopy (IR) 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 (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material [73].

Water Vapour Sorption: Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different [74].

This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

Isothermal Micro Calorimetry: Isothermal micro calorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg) [75].

This technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

Dissolution Calorimetry: Dissolution calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample [76]. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

Macroscopic Techniques: Macroscopic techniques that measure mechanical properties that are different amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity for and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solids.

Differential Scanning Calorimetry (DSC): Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC) [77]. 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. Thermal events can be a glass to rubber transition, (re) crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

Confocal Raman Spectroscopy: Confocal Raman Spectroscopy is used to measure the homogeneity of the solid mixture. It is described that a standard deviation in drug content smaller than10% was indicative of homogeneous distribution. Because of the pixel size of 2 μm3, uncertainty remains about the presence of nano-sized amorphous drug particles.

Temperature Modulated Differential Scanning Calorimetry (TMDSC): Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated.

For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC [78]. Therefore, this technique can be used to assess the amount of molecularly dispersed drug [79]. And from that the fraction of drug that is dispersed as separate molecules is calculated [80].

***In-vitro* Dissolution Studies:** *In-vitro* dissolution studies are done for the find out dissolution behavior. The *in-vitro* dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through in vitro – *in-vivo* correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed *in-vivo* dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. There are some apparatuses used in United States pharmacopoeia for dissolution testing these are following.

Solubility Studies: Solubility studies are done for the finding out the solubility behavior shown by the solid dispersion system in different types of solvent system and body fluids.

Application of Solid Dispersions [60, 72, 81]:

- Homogenous distribution of small amount of drug is obtained in solid state.
- In solid dispersions liquid and gaseous form are dispersed in solid form.
- Unstable formulations are stabilized using solid dispersions.
- In sustained released dosage form a fast release primary dose can be formulated.
- Presystemic inactivation of drug can be reduced like Morphine and progesterone.
- Incompatibilities which are undesirable can be avoided.
- Unpleasant and smell of drugs can be masked.
- Side effects of certain drugs can be reduced.
- Drug release from ointments, gels and creams can be improved.
- By using poorly soluble and insoluble carriers with soluble drugs a sustained release formulation can be formulated.
- Bioavailability, dissolution rate and absorption of the drugs can be increased by increasing the solubility of poorly water-soluble drugs.
- Chemical properties of drug are not changed.
- Solid solutions, isomorphs, eutectics, and other molecular additional compounds can be prepared from polymorphs.

TABLE 5: LIST OF DRUGS AND POLYMERS USED TO ENHANCE BIOAVAILABILITY OF THE POORLY SOLUBLE DRUGS

Sr. no.	Drug	Polymer/ Excipient	Reference
1	Glipizide, Rofecoxib, Piroxicam and Carvedilol	Cyclodextrin	Anuj Kumar, Review On Solubility Enhancement Techniques For Hydrophobic Drugs, Available online at www.pharmacie-globale.infoPharmacie Globale© (IJCP), 2(3).
2	Efavirenz	Starch phosphate	K.P.R.Chowdary, Enhancement of Dissolution Rate and Formulation Development of Efavirenz Tablets Employing Starch Phosphate a New Modified Starch ,IJPSDR April-June, 2011, 3(2), 80-83.
3	Meloxicam	PolyvinylPyrrolidone (PVP) and PEG 6000	Mohammed Jafar , Enhancement of Dissolution and Anti-inflammatory Effect of Meloxicam Using Solid Dispersions, International Journal of Applied Pharmaceutics, 2(1), 2010.
4	Rofecoxib	Polyethylene glycol 6000	Rakesh Kumar Sharma, Preformulation studies a view to develop fast release solid dosage, International Journal of Drug Delivery, 2, 2010, 32-36.

5	Gliclazide	(PEG)4000, PEG6000 and PVPK 30	Averineni Ranjith Kumar,Enhanced dissolution and bioavailability of Gliclazide using solid dispersion techniques, International Journal of Drug Delivery, 2, 2010, 49-57.
6	Ritonavir	Starch Phosphate	K.P.R.Chowdary and Veeraiah Enturi, Enhancement of Dissolution Rate and Formulation Development of Ritonavir Tablets Employing Starch Phosphate-A New Modified Starch, IJPSR, 2(7), 2011, 1730-1735.
7	Valsartan	Polyvinyl pyrrolidone, Hydroxypropyl β-Cyclodextrin, Hydroxypropyl methylcellulose	Amit R. Tapas, Spherically agglomerated solid dispersions of valsartan to improve solubility, dissolution rate and micromeritics properties, International Journal of Drug Delivery, 2010, 304-313.

CONCLUSION: There are many drugs having poor aqueous solubility and as dissolution of drug is the rate determining step for oral absorption of such drugs, which can subsequently affect the in vivo absorption of drug. So, to improve the aqueous solubility of the drugs, many techniques have been adopted since decades and solid dispersion is one of those techniques. Many techniques that can be used for the formulation of solid dispersion have already been discussed in the article. Third generation solid dispersions are mainly effective as they use many types of surface-active agents, they act as the plasticizers. Many dosage forms can be formulated by using the solid dispersion technology like tablets, capsules. Further research is also required for the better implementation of solid dispersion technology as this is an eminent technique for the solubility enhancement of poorly soluble drugs. Since the concept of solid dispersion technology was introduced in 1960s, great progresses have been made in solid dispersion technology as solid dispersion offers a variety of opportunities. A single solid dispersion method cannot be universally accepted for a variety of drug materials. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method. The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. Most of the solid dispersion work is in lab-scale setups; therefore, the manufacturing process requires enough knowledge to scale up to the commercial scale.

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