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SOLID DISPERSION – A PROMISING NOVEL APPROACH FOR IMPROVING THE SOLUBILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Solid dispersions is an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly soluble drugs. This article reviews the various types of solid dispersion, preparation techniques for solid dispersion and compiles some of the recent technologies. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization, along with nature of drugs in solid dispersions are also discussed. Finally, limited commercialization of solid dispersions and recent revival has been considered.

INTRODUCTION: Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate of extent of absorption of the drug.

When an active agent given orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. This article focuses on the former, in particular, the use of solid dispersion technologies to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability. In case of poorly water soluble drugs, dissolution may be the rate-limiting step in the process of drug absorption.

Drug with poor water solubility have been shown to be unpredictably and slowly absorbed compared with drugs of higher solubility. Therefore, a better oral, parenteral, or topical formulation can be developed by increasing the water solubility of the drugs. There are various techniques available to improve the solubility of poorly soluble drugs, such micronization, nanosuspension, modification of the crystal habits, eutectic mixtures, solid dispersions, micro emulsions, self micro emulsifying drug delivery systems, cyclodextrin inclusion and lipid based delivery systems etc. This review focuses on the solid dispersion

technique of solubilization for the attainment of effective absorption and improved bioavailability. Solid dispersion is one of the most promising approaches for solubility enhancement. In the biopharmaceutical classification system (BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs.

Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. An estimated 40% of these drugs are poorly water soluble. Although most of the drugs have encouraging experimental data obtained in vitro, the in vivo results have been disappointing.

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. In case of solid dispersion drug disperse in the matrix generally a hydrophilic matrix and a hydrophobic drug, 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 [1, 2]. There are various types of polymers, solvent used in formulations. List of commonly used ones are given in **table 1** & **2** and the list of poorly soluble drug used with which carriers is given in **table 3**.

TABLE 1: LIST OF CARRIERS USED IN SOLID DISPERSION

NATURE	CARRIER[15]
Acids	Citric acid, tartaric acid, succinic acid, phosphoric acid
Sugars	Dextrose, Mannitol, Sorbitol, Sucrose, Maltose, Galactose, Xylitol , Lactose, Soluble starch, D- glucose (Chitosan), Galactose, Xylitol, Galactomannan, British gum, Amylodextrin
Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000,PVP, CMC, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, ß- CD, HPß-CD, Eudragit® L100 sodium salts
Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Docusate sodium, Myrj-52, Pluronic-F68,SLS, Gelucire 44/14, Vitamin E TPGS NF
Hydrotropes	Sodium acetate, Sodium- o- hydroxy benzoate, Sodium- p- hydroxy benzoate, Sodium citrate, Resorcinol, Ascorbic acid
Dendrimers	polyamidoamine (PAMAM), Starburst
Others	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthenes, Microcrystalline cellulose, Dicalcium phosphate, Silica gel, Sodium chloride, Skimmed milk

TABLE 2: LIST OF SOLVENTS USED IN SOLID DISPERSION

SOLVENT	MELTING POINT (°C)	BOILING POINT (°C)
Water	0	100
Methanol	-93.9	65
Ethanol	-117	78.5
Acetic acid	17	118
1-propanol	-85	97.4
2-propanol	-127	82.4
Chloroform	-63	62
DMSO	19	189

TABLE 3: LIST OF POORLY SOLUBLE DRUGS WITH CARRIERS

DRUG	CARRIER
Griseofulvin	Polyethylene glycol (PEG)
Acyclovir	PEG, Urea, Mannitol, PVPK-30
Flufenamic acid	PVP
Aceclofenac	PEG, Urea, Mannitol, Lactose
Diazepam	Sodium salicylates
Glipizide	Urea, Polaxamer-188, PVP

Other drugs used are Diclofenac sodium. Isosorbide dinitrate, Rabiprazole, Atrovastatin, Simvastain etc. [6, 16].

"The term SD defined as the dispersion of one or more active ingredients (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid state prepared by the melting (fusion), solvent, or melting-solvent method". 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. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions. A solid dispersion is shown in **Figure 1**.

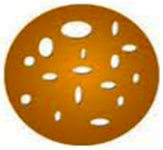

FIG. 1: SOLID DISPERSION OF API IN POLYMER MATRIX

Types of Solid Dispersion: Based on their molecular arrangement, six different types of solid dispersions can be distinguished as shown in **table 1** are;

TABLE 1: TYPES OF SOLID DISPERSION

Solid dispersion type	Matrix*	Drug**	Remarks No.	Phases	Reference
Eutectics	C	C	The first type of solid dispersion prepared	2	(Chiou and Riegelman, 1971)
Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2	(Breitenbach AH, 2002); (Mullins and Macek, 1960)
Solid solutions					
Continuous solid solutions	C	M	Miscible at all composition, never prepared	1	(Goldberg *et al.,* 1965]
Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed	2	Sekiguchi K and Obi N (1961)
Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 5% from the 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.	1 or 2	(Rastogi and Verma,1956); (Wilcox *et al*., 1964)
Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous.	2	(Chiou and Riegelman, 1971); (Chiou and Riegelman, 1969)
Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2	(Chiou and Riegelman, 1971); (Sarkari M et al., 2002)
Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2	(Chiou and Riegelman, 1971); (Sarkari M *et al*., 2002)
Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	1	Simonelli AP *et al*., 1969

***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, M: drug molecularly dispersed throughout the matrix**

Simple eutectic mixture:

1. Amorphous precipitations in crystalline matrix
2. Solid solutions;

i. According to their miscibility;
   a. Continuous solid solutions
   b. Discontinuous solid solutions

ii. According to the way in which the solvate molecules are distributed in the solvent;
   a. Substitutional solid solutions
   b. Interstitial solid solutions

3. Glass suspension
4. Glass suspension
5. Glass solution

Simple Eutectic Mixtures [3, 4]: When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability [5, 6]. The phase diagram for a eutectic system is shown in **Figure 2**.

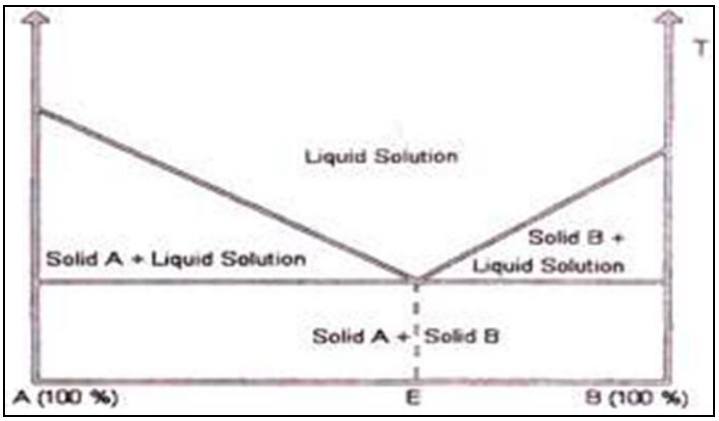

FIG. 2: PHASE DIAGRAM FOR A EUTECTIC SYSTEM

Solid Solutions: According to their miscibility two types of solid solution are;

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

Discontinuous Solid Solutions [6]: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease. According to Goldberg that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%, shown in **Figure 3**.

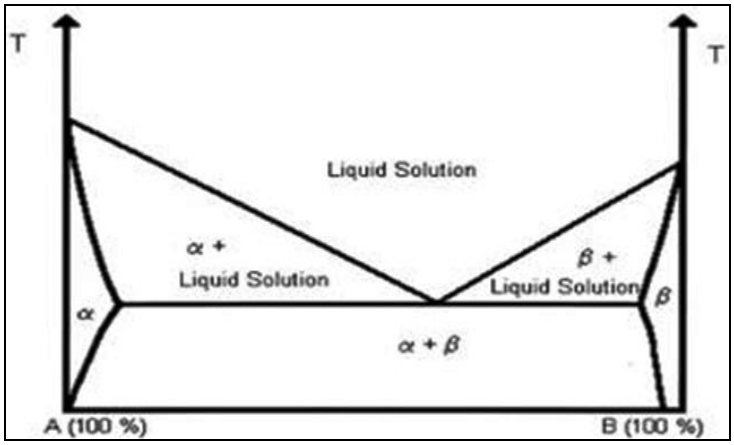

FIG. 3: PHASE DIAGRAM FOR DISCONTINUOUS SOLID SOLUTION

According to the way in which the solvate molecules are distributed in the solvent, the two types of solid solutions are:

Substitutional Crystalline Solutions: A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for solvent molecules in the crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules [7] shown in **Figure 4**.

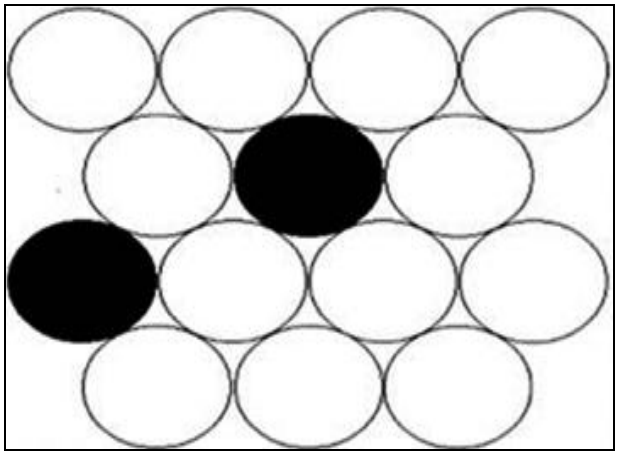

FIG. 4: SUBSTITUTIONAL CRYSTALLINE SOLID SOLUTION

Interstitial Crystalline Solid Solutions: In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent [8] shown in **Figure 5**.

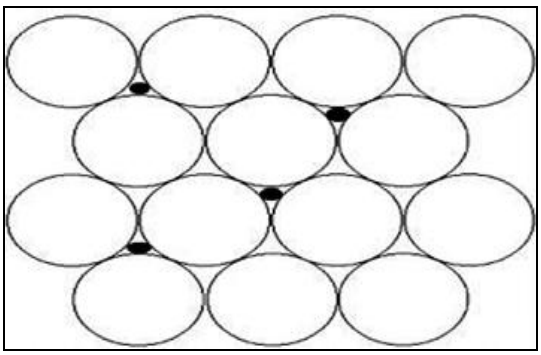

FIG. 5: INTERSTITIAL CRYSTALLINE SOLID SOLUTION

Amorphous Solid Solutions [9]: In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers urea and sugars such as sucrose, dextrose and galactose, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol and various cellulose derivatives have been utilized for this purposeas shown in **Figure 6**.

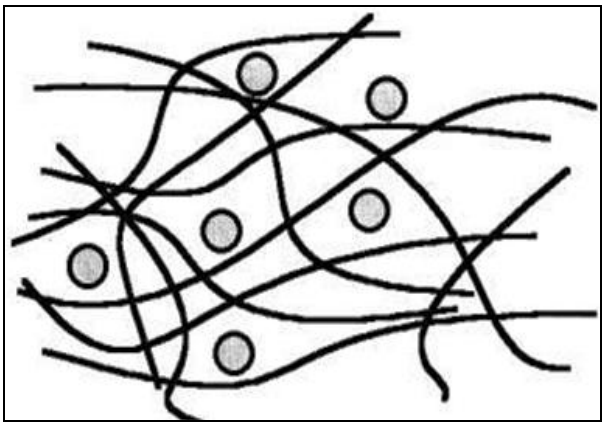

FIG. 6: AMORPHOUS SOLID SOLUTION

Glass Solutions and Glass Suspensions [8, 9]: Chiou and Riegelman first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The term glass can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency & brittleness below the glass transition temperature Tg.

Methods of Preparation:

Melting Method (Fusion Method) [4, 5]: The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. However many substances, either drugs or carriers, may decompose or evaporates during the fusion process which employs high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

Melt Extrusion Method [10, 11]: Melt extrusion method is same as the melt method except that intense mixing of drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.

Solvent Evaporation Method [12]: In this method, the first step is formation of solution containing physical mixture of the drug and carrier dissolved in a common solvent and second step involves the removal of solvent resulting in the formation of solid dispersion. First, to dissolve both the drug and the carrier in a common solvent and secondly, to evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic drug in the highly water soluble carrier polyvinylpyrrolidone.

An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65°C.

Melting Solvent Method (Melt Evaporation) [2, 5]: It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5-10% (w/w) of liquid compounds can be incorporated into polymer without significant loss of its solid property. It is possible that

the selected solvent or dissolved drug may not be miscible with the melt of the polymer. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg. The physical mixtures were prepared by weighing the calculated amount of drug and carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through 44-mesh sieve and stored in desiccators until used for further studies.

Co- Grinding Method [14]: The calculated amounts of drug and carriers where weighed and mixed together with one ml of water. The damp mass obtained was passed through a 44-mesh sieve; the resultant granules were dispersed in Petri dishes and dried at 60°C under vacuum, until a constant weight was obtained. The granules obtained were stored in desiccators until used for further studies.

Methods for the characterization of Solid Dispersions:

Particle Size: Scanning electron microscopy (SEM) polarization microscopy method is used to study the microscopic surface morphology of drug and carriers and sometimes the polymorphism of drug. The fine dispersion of drug particles in the carrier matrix may be visualized.

Dissolution Testing: Drugs having intrinsic dissolution rate < 0.1 mg/cm^2//min usually exhibit dissolution rate limited absorption. Comparison of dissolution profile of drug, physical mixtures of drug and carrier and solid dispersion may help to indicate the mechanism of improved release of drug in the formulation (solubilization / wetting / particle size reduction).

Infrared Spectroscopy: Infrared spectroscopy (IR) helpful in determining the solid state of the drug (molecular dispersion, amorphous, crystalline or a combination) in the carrier regardless of the state of the carrier. Crystallinities of under 5-10% cannot generally be detected. It also used to study the interaction occur between drug and polymer by matching the peaks of spectra. The absence of any significant change in the IR spectral pattern of drug & polymer physical mixture indicated the absence of any interaction between the drug and the polymer.

Differential Scanning Calorimetry: A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC) [17]. It help to study the changes in the physical state of solid dispersion may occur during heating, and the presence of polymer may influence the melting behavior of drug (e.g. melting point depression). Results need to be confirmed by another technique. Crystallinities under 2% cannot generally be detected.

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. Recently developed X-ray equipment is semi quantitative.

Advantages of Solid Dispersion:

Generally, solid dispersion is mainly used

- To reduced particle size
- To improve wetability
- To improve porosity of drug
- To decrease the crystalline structure of drug in to amorphous form
- To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical
- To mask the taste of the drug substance
- To prepare rapid disintegration oral tablets.

Reduced Particle Size: 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 [18]. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability [19].

Improved Wetability: The enhancement of drug solubility is related to the drug wetability improvement verified in solid dispersions [20]. It was observed that even carriers without any surface activity, such as urea [4] improve drug wetability. Carriers with surface activity, such as cholic acid and bile salts when used, can significantly increase the wetability property of

drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects [19, 21].

Increase Porosity: Particles in solid dispersions have been found to have a higher degree of porosity [23.] The increase in porosity also depends on the carrier properties, for example, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate[24]. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in Amorphous State: Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility [25]. 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 [26]. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution; if drugs precipitate it is as a metastable polymorphic form with higher solubility than the most stable crystal form [18, 19].

For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

Alternative Strategies:

Lyophilization Technique: Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. 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 [27].

Spraying on Sugar Beads using Fluidized Bed Coating: The approach involves fluidized bed coating system, where-in a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step. This method has been applied for both controlled-and immediate-release solid dispersions [28]. For e. g., Itrakanazole 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.

Direct Capsule Filling: The filling of semi solid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in1978. Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (e.g., poly-sorbate80 with PEG, phosphatidylcholine with PEG). The temperature of the molten solution should not exceed ~70-C because it might compromise the hard-gelatin capsule shell.

The use of Surfactant: The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobisity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions.

Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions. Two of the important surface-active carriers used are Gelucire 44/14and Vitamin ER-alpha- tocopherylpolyethyleneglycol 1000 succinate (TPGS). In which Gelucire44/14 has commonly been used in solid dispersion for the bioavailability enhancement of drugs. A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-active carrier [29, 30].

Electrostatic Spinning Method: This technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology

[31]. This technology is now applied in the pharmaceutical field [32]. Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. 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 [33]. Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (biodegradable and non-biodegradable) 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 [34].

Super Critical Fluid (SCF) Technology: This technology has been introduced in the late 1980s and early 1990s, From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded biopolymer micro-particles for pharmaceutical applications has been studied intensively by a number of researcher groups CFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS).

Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance. In the supercritical fluid carbon dioxide is used used as either a solvent for drug and matrix or as an anti-solvent [35]. When supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO2 of most pharmaceutical compounds is very low (<0.01wt-%) and decreases with increasing polarity [36].

Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system (ASES), precipitation with a compressed fluid antisolvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical anti-solvent (SAS). The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient.

In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component).

CONCLUSION: The solubility of the drug is the factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. There are various available techniques, alone or in combination can be used to enhance the solubility of the drug. Although in all techniques mentioned solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited.

Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

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