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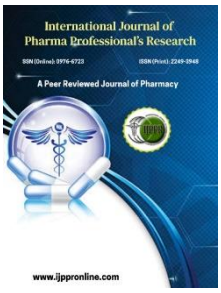

Solubility Enhancement of Poorly Water-Soluble Drugs by Solid Dispersion Techniques

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ABSTRACT: The fact that newly discovered API's (about 90%) or new molecular entity (NME) have little or poor aqueous solubility, causes a significant challenges to the initialization of development and commercialization of dosage form at the manufacturing facility. Poor aqueous solubility of API's has critical role in drug dissolution or availability of drug at the site of actionor bioavailability, when a dosage form is administered orally. Various techniques are available for the enhancement of solubility but all individual techniques have its own limitations for commercialization. The known Solubility enhancement techniques like Solid dispersions involved the dispersion of poorly soluble drug in a suitable inert carrier at a molecular level and form amorphous and highly soluble compounds. The conversion of compound in to amorphous form or reduction of particle size to its molecular level caused enhanced solubility of poorly soluble by the application of solid dispersion techniques.

Introduction: The oral administration is still widely acceptable drug delivery route because of its manifold applications along with simplicity of ingestion, versatility, cost effectiveness, flexibility of dosage form design and most important high patient acceptability.[1] Poor aqueous solubility of API's plays a vital role in drug dissolution or absorption of the drug from the oral dosage form and ultimately its bioavailability. When a drug is administered in solid dosage form, it is designed to undergo series of predetermined stages. The first step towards the absorption process is the disintegration or diffusion/ erosion of drug from a dosage form. The second step is slowest or rate-limiting step includes dissolution of drug in the fluid at the absorption site (Figure 1). The fact that most of the newly discovered API's or new molecular entity (NME) have little or no aqueous solubility and are responsible for

commercialization or development of further molecules in the dosage form. Although the pharmaceutical companies have been able to overcome difficulties with very slightly soluble drugs, but those with aqueous solubility of less than 0.1 mg/ml causes some unique challenges.[2,3]

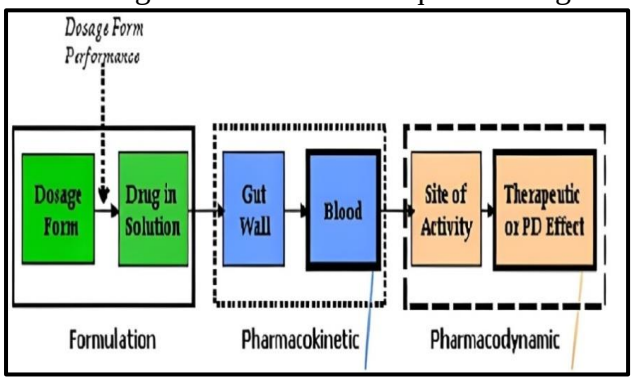

Figure 1. Schematic representation of oral dosage form and its absorption

When solubility of API's or dissolution is the rate-controlling step in the oral administration process, absorption of drug is said to be dissolution rate-limited. Hence, dissolution of drug is the rate-limiting step in the absorption process and factors which can influence dissolution rate can also influence the absorption rate. Dissolution theory states[4] that, dissolution rate of an API's in a particular medium are prominently related to:

a) The solubility of the API's in the medium, where dissolution carried out and
b) The particle size or active surface area of the API's, which are directly bring in contact with dissolution medium.

The availability of drug at the absorption site is the controlling factor for the successful development and commercialization of a pharmaceutical product in any pharmaceutical industries. Hence, a development of NME's becomes difficult and their potential are not realized or confirmed.[5,6] According to the Biopharmaceutical Classification System (BCS)[3,7-12] drug substances are generally classified into four categories (Figure 2) upon their solubility and permeability:

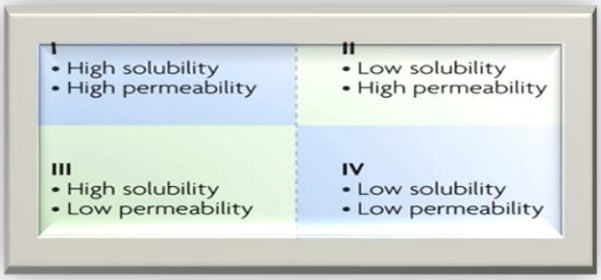

Figure 2. Biopharmaceutical Classification System (BCS)

The solubility of drug/NME's is defined as the amount of drug that goes into solution when equilibrium is established between the drug solute in solution and any excess, un-dissolved drug to produce a saturated solution at a specified temperature. When the highest dose strength of API's is not completely soluble in aqueous media (volume 250 ml over the pH range of 1.2 to 6.8), the NME's is considered as poorly aqueous soluble.[10-13] The United State Pharmacopeias(USP)also define solubility (Table 1) as a part of solvent required per part of solute:[14]

Table 1: USPNF Solubility Criteria

Solubility Criteria [as per United States of Pharmacopeias(USP)]		**Solubility (mg/ml)**
Terminology	**Part of solvent required per part of solute for solubilization**	
Very soluble	< 1	> 1000
Freely soluble	1 to 10	100 - 1000
Soluble	10 to 30	33 – 100
Sparingly soluble	30 to 100	10 - 33
Slightly soluble	100 to 1000	1 – 10
Very slightly soluble	1000 to 10,000	0.1 – 1
Practically insoluble	≥10,000	< 0.1

BCS class II & class IV drug candidates have poor aqueous solubility and need a solubility enhancement approach for successful development& commercialization of oral dosage form with enhanced bioavailability.[9-12,15] Hence, enhancement in drug solubility is an essential requirement for a development of a product. Numerous technologies have been work out in the recent past. A lot of approaches are being currently used for the solubility enhancement of poorly aqueous soluble drugs.[12,13,15,16] Some applicable approaches are as per following (Table 2):

Table 2. Solubility enhancement techniques

Approaches		
Physical	***Chemical***	***Miscellaneous***
1. Particle Size Reduction ➢ Conventional Method or Grinding ➢ Micronization or Milling ➢ Nanoparticle or Nanosuspension 2. Crystal Habit Modification ➢ Polymorphs ➢ Pseudopolymorphs 3. Complexation ➢ Physical Mixture ➢ Kneading Method ➢ Co-precipitation Method 4. Inclusion Complexation ➢ Kneading Method ➢ Lyophilization ➢ Microwave irradiation Method 5. Surfactant based Solubilization ➢ Microemulsion 6. Solid Dispersion ➢ Physical Kneading ➢ Melting /Fusion ➢ Solvent Evaporation ➢ Spray Freeze Drying ➢ Hot melt Extrusion	1. Pro drug approach 2. pH Adjustment 3. Buffer balance 4. Derivatization, 5. Salt formation. 6. Polymeric micelles formation 7. Self-emulsifying systems	1. Supercritical fluid process, 2. Adsorption

Out of these various approaches, physical approach like Solid dispersion is being broadly utilized for solubility enhancement. This approach is briefly highlighted below:

2. Solubility Enhancement by Solid Dispersion Technique: Solid dispersion is a prominent approach for enhancement of solubility, dissolution rate and bioavailability of drugs which have limited aqueous solubility. Solid Dispersion can be defined as a "dispersion of one or more active ingredients at molecular to microcrystalline level in an inert carrier or matrix at solid state". Physiologically inert carrier is used for the preparation of solid dispersion and it may be readily water-soluble carrier or water insoluble carrier, for fast or modified release preparations respectively.[2,3]

Solid dispersion concept was first introduced in 1961 by Sekiguchi and Obi scientists.[17] They

prepared a solid dispersion of sulfathiazole with Urea as a water-soluble carrier by melting the physical mixture of sulfathiazole and urea (eutectic mixture), followed by a rapid solidification by cooling them. The prepared material was identified the higher absorption of sulfathiazole after its oral administration as compared to sulfathiazole alone.[17]

In 1971, Chiou and Riegelman defined the term "solid dispersion". According to author Chiou it is as "a 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".[18]Solid dispersion may also be called' solid-state dispersion".[19] Fusion process also called melts and solvent method are frequently referred to as 'coprecipitates' (Sulfathiazole-PVP dispersion)[20] or 'coevaporates' (Reserpine-PVP Dispersion).[21] Numerous techniques are employed for preparation of solid dispersion which has been briefly and critically reviewed in this article. In general, Solid dispersions are classified on the basis of Carrier used in the preparations and their molecular arrangement.

3. Classification of Solid Dispersion on the basis of their molecular arrangements: Chiou and Riegelman classified the solid dispersion into six groups, namely.

3.1 Simple eutectic mixture: A eutectic mixture consists of two independent components, both components are completely miscible in the liquid state but they are miscible in the solid state at a limited extent.[22] Eutectic mixtures are produced by chilling or quenching of melt mixture of components which, produces very fine crystals. A simple eutectic mixture is represented in Figure 3, where both component A & B are not miscible in solid state. When this mixture is heated and cooled, it produces very fine crystals and its larger surface area are responsible to improve dissolution rate and ultimately improved bioavailability.[18,22]

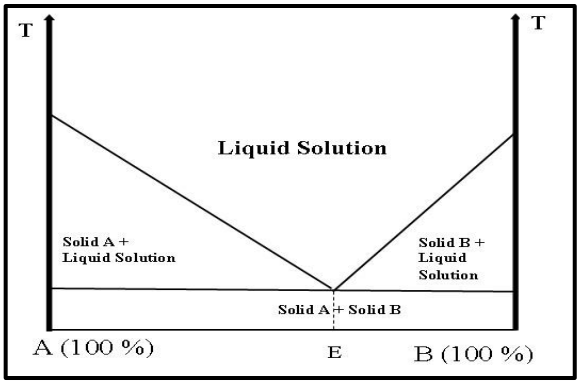

Figure 3. Phase diagram of simple eutectic mixture

3.2 Solid solutions: Solid Solutions are similar to liquid solutions. They consist of only one phase, where two components are crystallize together in a homogenous one-phase system. This Solid solution reduces the particle size up to the molecular size. Hence, faster dissolution can be easily attained in comparison to eutectic mixture.[18, 22-24] Figure 4 shows various types of solid solution.

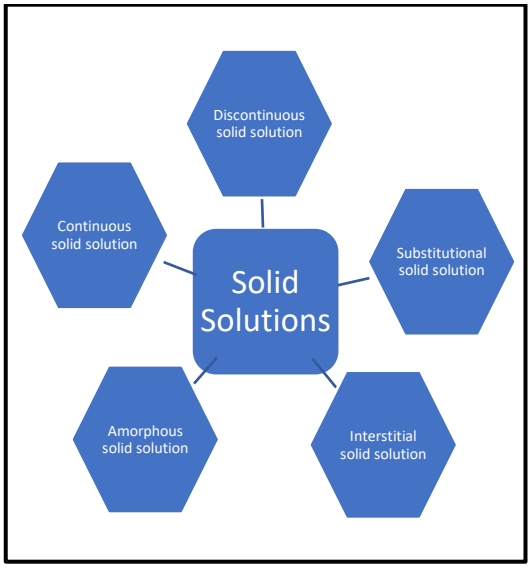

Figure 4. Types of Solid Solutions

3.2.1 Continuous solid solutions: Two components are miscible or soluble at solid state in all proportions (Figure 5) in a continuous solid solution. This type of solid solution is not reported in literature.[18,22]

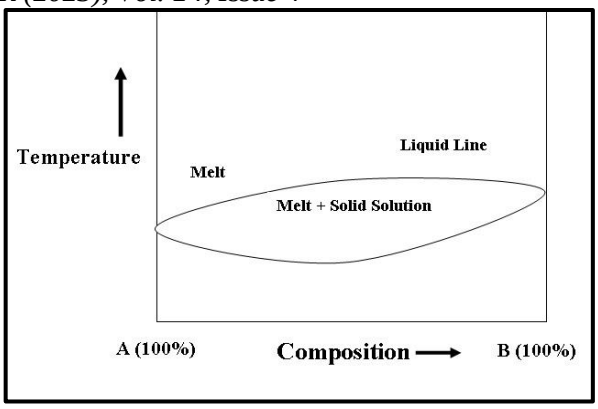

Figure 5. Phase diagram of continuous solid solution for a binary system consisting of A and B

3.2.2 Discontinuous solid solutions: This system has only a limited solubility of a solute in a solvent system in comparison to continuous solid solution (Figure 6).[22]

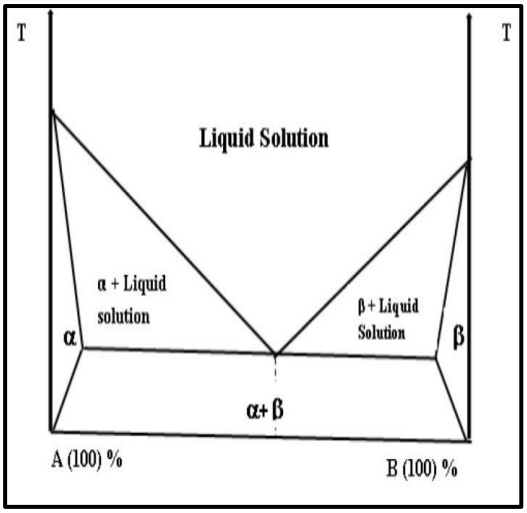

Figure 6. Phase diagram of a Discontinuous Solid Solution for a binary system consisting of A and B, where α and βare regions of solid solution formulation

3.2.3 Substitutional crystalline solid solutions: In substitutional crystalline solid solution, some of the solvent molecules are substituted by solute molecules in the lattice of crystalline molecules (Figure-7). The requirement for this type of solid solution is when solute molecules sizes are differed below 15% from the lattice of solvent.[22]

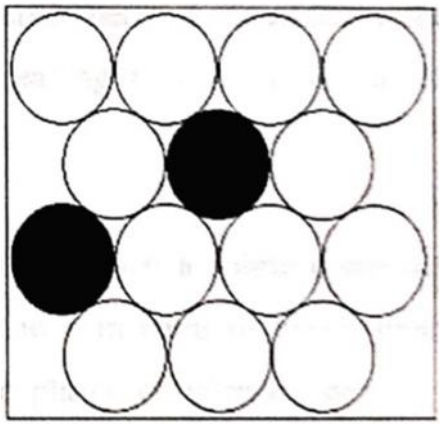

Figure 7. Substitutional Crystalline Solid Solution

3.2.4 Interstitial crystalline solid solution: The solute molecules occupy the interstitional space (Figure 8) in the solvent lattice and produces interstitial crystalline solid solution.[18, 22]

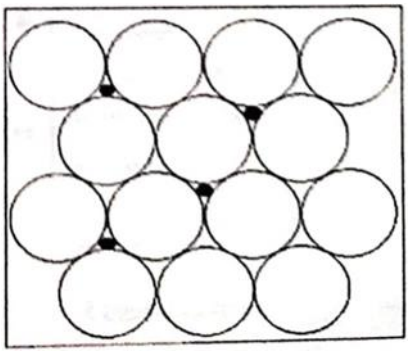

Figure 8. Interstitial Crystalline Solid Solution

3.2.5 Amorphous solid solution: The irregularly and molecularly solute molecules are dispersed within the solvent and produce amorphous Solid Solution (Figure-9). Solute molecules plasticize the polymer and amorphous polymer chain network. Hence, ultimately reduction in its glass transition temperature.[18,22]

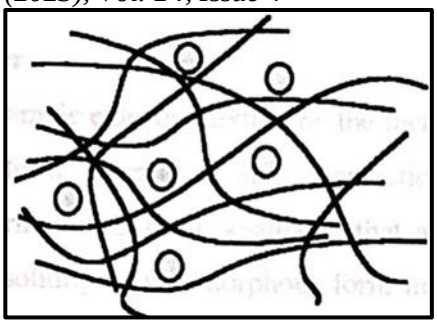

Figure 9. Amorphous Solid Solution

3.3 Glass Solution and Glass suspension: Solute is dissolved in the Glassy carrier and produces a homogenous glassy system called 'Glass solution'. Whereas 'Glass Suspension' refers to a mixture in which precipitated particles are suspended in a glassy solvent. An abrupt quenching of the melt produces a glassy or vitreous state. Transparency and brittleness below the glass transition temperature (Tg) can characterized this state. The lattice energy represents a barrier for rapid dissolution in glass solution. Figure 10 shows the volume changes associated with glass formation when a melt is cooled down. Carriers that form glass solution or glass suspension include citric acid, sugars, polyvinylpyrrolidone, urea and polyethylene glycol.[18,23,24]

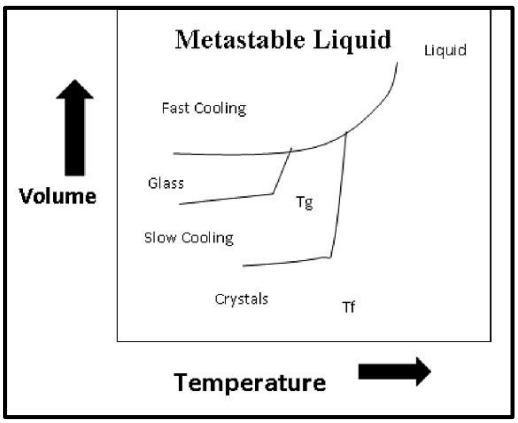

Figure 10. Temperature volume changes associated with cooling of melts

3.4 Amorphous precipitation in crystalline carrier: This type of solid dispersion shows precipitation of drug in an amorphous form as compared to simple eutectic mixture, whereas drug is precipitated out in crystalline form. It has been postulated that a drugs super-cooling property has more tendency to solidify as an amorphous form in the carrier.[18,23,24]

3.5 Compound and complex formation between drug and carrier: Compound and complex formation (soluble and insoluble) can enhance or reduce the dissolution of drugs. e.g. Quinine-Phenobarbitone system increases dissolution, whereas PEG-Phenobarbitone system reduces the dissolution.[18,23]

3.6 Any combination of above classes: It is also possible that, solute molecules can exist in combination of above classes in the form of crystalline or amorphous forms.[18,23]

4. Classification of Solid dispersion based on carrier used: Solid dispersion is also classified in four categories as per the carrier used.[25,26] Table 3 highlighted different generation of Solid dispersions. Whereas Table 4 highlighted different category of carriers used for the preparation of Solid Dispersion.[25,27,28]

Table 3. Types of Solid dispersion based on carrier system

Solid Dispersion Types	Carriers	Characteristics
First Generation	Crystalline Carriers like Sugars, Urea etc	Enhancement of Solubility & dissolution by decreasing size of API particles or increasing their surface area, improving water uptake capacity and change in their polymorphicforms.

Second Generation	Amorphous carrier likes Synthetic or natural polymers; Hydroxypropyl methyl cellulose (HPMC), Polyethylene glycol (PEG), Povidone, Hydroxy ethyl cellulose (HEC), Starch, Cyclodextrin, PVP, EC, HPMCS	Amorphous nature of carrier increases wettability, dispersibility of the crystalline drug and decrease their crystalline nature on dissolution in aqueous media. The low thermodynamic stability of carrier is a main characteristic of high dissolution rate.
Third Generation	Carriers with additional surface-active agents or self emulsifiersexamples include Poloxomer, Gelucire, Soluplus, Sodium Lauryl sulfate, Tween 80 and compritrol	They are used to achieve highest degree of bioavailability, to stabilize solid dispersion and avoid drug recrystallization.
Fourth Generation	A wide range of Water-soluble polymers or water insoluble carrier or swellable carriers like Ethy Cellulose, Carbopol, Polyethylene oxide (PEO), Eudragit and carboxyvinyl polymer	Applicable for drugs having low aqueous solubility, short biological half-life and to obtain a sustained or controlled release pattern.

Table 4. Category of carriers for the preparation of solid dispersion

Categories	**Examples**
Sugars	Sugar alcohols like Lactose monohydrate or Lactose anhydrous,Fructose,Sucrose, Dextrose, Galactose, Maltose, Sorbitol and Xylitol, Amylodextrin, British gum, galactomannan and Mannitol, etc.
Acids	Acids Like Citric, Tartaric, Succinic, phosphoric and/or their combinations etc.
Polymeric materials	Carregeenan, Pectin, Polyvinylpyrrolidone (PVP), Poly(vinyl alcohol) (PVA), polyether compound like Polyethyleneglycol (PEG 6000 or PEG 8000), HydroxyPropyl Methyl Cellulose (HPMC), Gelatin, Ethylcellulose (EC), Methyl cellulose (MC), HydroxyEthyl Cellulose (HEC), HydroxyPropyl Cellulose (HPC), Sodium carboxymethyl cellulose, Sodium Alginate, Galactomannan, Dextrins, Cyclodextrin (CD) and its derivatives, Gum Arabic, Tragacanth, and Guar Gum etc.
Insoluble or enteric polymers	Hydroxypropylmethyl cellulose phthalate (HPMCP),Polymethylacrylate (e.g. Eudragit L-100, Eudragit S-100, Eudragit RL, Eudragit RS), Poly DL-aspartic acid and Spheron P40 etc.
Surfactants	Non-ionic surfactantlikePolyoxyethylene stearate, Synthetic block copolymers(Pluronic F 68), water-soluble nonionic triblock copolymers (Poloxamer 407&Poloxamer 188, mixtures

	of mono, di and triglycerides with PEG esters of fatty acids(Gelucire 44/14), docusate sodium, Texafor AIP, Deoxycholic Acid, Tweens, Spans, Myrj 52, Myrj 51, Myrj59, Polyoxyethylene 40 Stearate (P40S) and Brij 35 etc.
Miscellaneous materials and Combinations	Pentaerythritol, Pentaerythrityltetraacetate, Urea, Urethane, Hydroxyalkyl-xanthines, Dehydroxypropyltheophylline, Nicotinamide, Hydroquinone, Ascorbic Acid, Acetamide, Nicotinic Acid, Succinamide, mixture of sugar like Sugars-PEG and Surfactants like Sterol etc.

Hence, Solid dispersion enhances the dissolution rate of poorlysoluble drugs due to following reasons:[18, 24-26, 28,29]

a. Particle size reduction of API at their molecular level,
b. Hydrophilic nature of carrier or high wetting of API molecules resulting high dissolution rate,
c. Conversion of crystalline compound into amorphous state.

5. Solid Dispersion Preparations Method: There are numbers of approaches (Table 5) for the preparations of solid dispersion, some are briefly but critically reviewed in this article:[24,26,28-30]

Table 5. Solid Dispersion Methods

S. No.	Solid Dispersion Methods
1.	Melting/ Fusion method
2.	Solvent method (including Spray drying and Freeze drying)
3.	Solvent-melting method.
4.	Co-milling
5.	Coprecipitation or Coevaporate Method
6.	Kneading Method
7.	Hot-melt extrusion
8.	Hot-spin-melting
9.	Supercritical fluid process (SCF)
10.	ElectrostaticSpinning Method
11.	Microwave irradiation technique

5.1 Melting/ Fusion Method: A physical mixture of an active agent and a carrier is heated up to its melting. The melted physical mixture is solidified rapidly in an ice bath or in liquid nitrogen under rigorous stirring, then pulverized and sieved to obtain a desired particle size. The molecular dispersion of dispersed drug can be achieved by rapid cooling leads to super saturation and solidification.[17,18,31-33] Advantages & disadvantage of melting methods are highlighted in Table 6.

Table 6. Advantages & Disadvantage of Melting Methods

Advantages of melting method	Disadvantages of melting method
i) Simplicity of process, ii) Economicity, iii) No need of Solvent.	i) This method is not suitable, if the drug or carrier is unstable at fusion temperature or evaporates at higher temperature (e.g. succinic acid) i.e. thermo stability of drug and carrier is essential. ii) Miscibility issue of both drug and carrier during melting, iii) Tacky and intractable nature of solidified melt, iv) Irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug-carrier system, v) Sublimation, polymorphic transformation and

	metastable modification of drug may be formed, which convert more stable forms during storage, vi) Solidification temperature will affect crystallization rate and may alter both the crystal size and the hardness of the dispersion.

5.2 Solvent Method: The drug and carrier molecules are initially mixed in a solvent (organic solvents). Tachibana and Nakamura firstly used this method to prepare solid dispersion of β-carotene in Polyvinylpyrrolidone using chloroform as a cosolvent.[18,32] The solvent choice with its removal rate isessential to the standard of formed dispersion. In this method temperatures are used in the range of 20-65°C for completely evaporation of organic solvent. Various method can be used for solvent evaporation likes vacuum drying, rotary evaporators, spray drying and freeze-drying process. Advantage and disadvantages of solvent method are as per following:[52,54-64]

Table 7. Advantages & disadvantage of solvent methods

Advantages of melting method	Disadvantages of melting method
i) Suitable for the drugs and carrier which are sensitive for thermal decomposition, ii) Suitable for high melting point carrier.	i) Higher cost of production, ii) Consumption of huge amount of organic solvent and their complete removal from solid dispersions, iii) Possible adverse effects of residual solvent, iv) Selection of common volatile solvent, with negligible toxicity for a hydrophobic drug and hydrophilic excipient; polarity of both components, v) Difficult to reproduce crystal forms, vi) Inability to attain supersaturation of the solute in the solvent system unless the system goes through a highly viscous phase, vii) Environmental hazards, viii) Residual solvent can plasticize the dispersion and can alter physiochemical properties, ix) Explosion problem due to volatile nature of solvent.

5.3 Solvent-Melting method: In this method small volume of organic solvent are used to dissolve the drug, then the solution is added to molten carrier and the resultant solution is evaporated to dryness. Thermolabile and high melting points drugs are suitable candidate for this method. Such a unique method possesses advantages of both melting and solvent methods. Unfortunately, this method is limited for therapeutic dose below 20 mg. The feasibility of method has been demonstrated for spironolactone dispersion in PEG6000.[18]This method has no or limited industrial applicability as addition of

organic solvent in a melted carrier is cautionary.[28,32, 38,39,43]

Advantages of Hot-Melt Extrusion method	Disadvantages of Hot-Melt Extrusion method
i) Consistent, Reproducible and Cost-efficient process, ii) High mechanical energy input makes it efficient melting with low drug degradation, iii) Enclosed environment with nitrogen flushing makes it an oxidation free process and suitable for drugs which are prone to oxidation, iv) No requirement of Solvent, v) Applicable for thermolabile polymer or drugs, vi) Automation process, vii) Ability to produces dense compact material for formulation of tablet dosage forms.	i) High production cost ii) Consumption of huge amount of organic solvent and their complete removal from solid dispersions, iii) Residual solvent adverse effect iv) Selection of common volatile solvent, with negligible toxicity for a hydrophobic drug and hydrophilic excipient; polarity of both components, v) Difficult to reproduce crystal forms, vi) Inability to attain supersaturation of the solute in the solvent system unless the system goes through a highly viscous phase, vii) Environmental hazards, viii) Residual solvent can plasticize the dispersion and can alter physiochemical properties, ix) Explosive process.

5.4 Co-milling or Grinding method: The drug and carrier are milled in a mortar pestle or in a ball mill. Milling process causes disorganization of crystal molecules leads to heat generation or melting and produces amorphous materials.[28,33,38,39]

5.5 Coprecipitation or Coevaporate Method: Coprecipitation method involves, dissolution of drug in an organic solvent and carrier in water. The aqueous carrier solution is finally added in to the organic drug solution and concurrent precipitation of the dissolved components by the addition of anti-solvent. The precipitate is filtered, washed and evaporated to remove traces of organic solvent. Finally, the precipitate is dried and sized.[26,28,33,44]

5.6 Kneading Method: Kneading method involves, kneading, mixing or triturating the drug and carrier in the presences of minimum amount of water or organic solvent. The incorporated amount of water or solvent is removed by any means of convenient drying method and dried dispersion is finally sized to produce a fine solid dispersion.[28,33]

5.7 Hot-Melt Extrusion (HME): Extrusion produces uniform shape and density of a product when it passed through a die under a variety of controlled conditions.[45] HME is a common method in polymer industry of producing plastics. Scientists, Speiser and Hiittenrach were firstly introduced or apply it in a pharmaceutical purpose. Presently, it is used in the preparation of Solid Solutions. The principle of the method is a mechanical mixing &melting of solids together. It has vast advantages& disadvantages (Table 8).[26,33,42,45-48]

Table 8. Advantages & disadvantages of hot-melt extrusion methods

Main disadvantage of this method is requirement of large quantity of materials at an early drug development stage.[48] HME technique is generally used in polymer industry. In a pharmaceutical industry, poorly soluble drugs with a suitable carrier are processed through a twin-screw

extruder. The physical mixture of drug and carrier are mechanically mixed, melted simultaneously and then extruded through a die to form suitable-sized granules or pellets.[45,48] The examples of HME are troglitazone-PVP and a sustained-release tablet of verapamil (ISOPTIN SR).

Following are the requirements for the drugs as well as polymers to be used in this method are:[46-48]

- Drugs with a higher melting point may be good candidate if the polymer has a lower glass transition or low melting point.
- Drugs with lower melting point can be used with a higher glass transition polymer.

5.8 Hot-Spin-Melting: This is another method for processing of thermolabile drug substances. Melting and spinning of physical mixture is carried out in a closed chamber for a very short duration of time and then dispersing the melted mass in air or an inert gas in a cooling chamber. Examples of drugs which are used in this method are testosterone, progesterone and dienogest.[22,50]

5.9 Supercritical Fluid Process (SCF): Supercritical fluid technology has been commercial use for past 30 years as an environmentally friendly, energy and cost saving tool in various industries. The process was developed by Ferro Corporation and consists of various steps including:[18]

- Introducing a suitable polymer anda bioactive material in an autoclave under mechanical stirring,
- Swelling of polymer by application of Supercritical CO_2 under specific condition of temperature and pressure,
- Rapid depressurization of the autoclave vessels through a computer-controlled orifice produces desired particle size,
- The mild temperature condition (35-75°C) makes it suitable for heat sensitive biomaterials, such as enzyme and proteins.

This technique was particularly used for decaffeinating coffee, tea and for the extraction of flavors and essential oils from natural sources. Therefore, supercritical carbon dioxide has favorable properties of being nontoxic and inexpensive makes it an alternate of solid dispersion preparation by solvent method.[26,28,30,33,38,39]

For the preparation of Solid dispersion, drug and polymer are dissolved in supercritical CO_2 and blasted into a low-pressure zone through a nozzle to generating adiabatic CO_2 expansion and fast cooling. Hence, this approach can create drug particles with much smaller particle sizes. It is an environmentally friendly process, because of no use of organic solvents and with patient compliance (due to small amount of residual CO_2 trapped inside the polymer).[33,38,39] Advantages & disadvantages of Supercritical fluid process are shown in Table 9.

Table 9. Advantages & disadvantage of supercritical fluid process

Advantages of Supercritical fluid process	**Disadvantages of Supercritical fluid process**
i) Suitable for thermolabile drugs. ii) Produces solvent free solid dispersions. iii) Higher solute throughput.	i) Limited solubility of most of the pharmaceutical powder in $CO_2$and prevents this method from being used in practice.

5.10 Electrostatic Spinning Method: Electrostatic Spinning Method is primarily used in the polymer industry and it is a combination of solid dispersion and nanotechnology. This method consists of a spinneret, connected with a micro syringe pump filled with anorganic solvent containing drug-polymer mixture. Micro syringe pump is also connected with a tip of the needle to raise a charge on the solution surface. A charge on the solution surface can be released by applying a high voltage current (5 to 30kV) to the needle tip. From a fixed distance in between spinneret and collector, a set electrical potential is also applied

which potentiates the solution to come out and fast evaporation of solvent produces a micron or submicron size diameter fibers. These fibers are further accumulated on a mandrel or screen. Various factors that affect the fiber diameter are electric field strength, solution surface tension, dielectric constant and feeding rate. The high surface area of fiber makes it a fast and efficient solvent evaporation method. The improved solubility and bioavailability of poorly soluble drugs is due to amorphization and nanosizing of drug incorporated in the fibers.[26,30,37]

5.11 Microwave Irradiation Technique: Microwave energy is used in Microwave irradiation technique for the formulation of amorphous type Solid Dispersion. An electromagnetic irradiation of frequency between infrared and radio frequency in a range of 0.3 to 300GHz is called Microwave irradiation. When the microwave energy is applied on a physical mixture of drug and polymer, it causes heat generation and melting of sample. The molecules are characterized by the presence of dipole moment, where absorbed microwave energy generates heat in the molecules. This technique has characteristics unique advantages over other conventional methods like low thermal energy, high penetration in a short time duration and preparation of amorphous solid with improved drug solubility & bioavailability.[26,28,37]

6. Some Patented Solid dispersion Technologies: This manuscript briefly highlights some patented solid dispersion technologies:

6.1 Meltrex™: This is a patented technology and trademarks of the Abbott group of companies. This technique is based on Hot-melt extrusion principle and used for thermolabile, oxygen sensitive and moisture sensitive drugs. This technology utilizes special designed twin screw extruder attached with two separate hoppers for transferring the material to the extrusion port continuously. This technique has unique advantages of low resistance time of thermolabile drug in extruder and avoids thermal stress. Due to a compact closed chamber manufacturing process, this technique is used forheat sensitive, oxygen sensitive and hydrolysis sensitive materials.[26,30,39,51]

6.2 Kinetisol® dispersing technique: KinetiSol® Technology was developed by AustinPx™ Georgetown and is a fusion-based technique, where both frictional and shear energies combined for efficient mixing to produce a homogenous mixture of drug-polymer in a molten stage. A computer-control module is used to control temperature and time of process to produces molten matrix. This technique has very low processing time; less than 20 seconds and has capability to produces an amorphous solid dispersion of broader formulation design space (high melting point & poor solvent solubility of active pharmaceutical ingredients), viscous polymer, very low processing time, solvent free process and wide application to challenging molecules.[26,30,33,37,52]

6.3 Solumer®: It is a patented technology of Formulex Pharma Innovations Ltd, Israel. Technique is based on interaction of insoluble-lipophilic molecule with polymers resulting in a solid composition. Lipophilic compound dissolves faster and to a higher extent, enhancing the drug solubility and bioavailability in aqueous media. Formulex Pharma has been developing more than 10 medical cannabis products using their patented Solumer™ and generic technologies. Five of the products are under the clinical and commercial stages.[30]

6.4 Hovione: Hovione is a developing company and particularly specializes in process development technology & scale up processofparticle engineering. This technique providesasolution for oral bioavailability, lung delivery, modified release, taste masking and it support proof of concept to commercial large-scale manufacturing. Hovione provides services to the pharmaceutical industry in solid dispersion technologies since last 15 years. It is engaged in various technologies of

solid dispersions like HME, Spray drying, Jet milling, Nanoparticles and Spray congealing technologies. It also provides all the way of manufacture to commercial supplies and performs formulation development and production of early clinical supplies. It works on mathematic modeling concept to understand the fundamentals of the solid dispersion process and uses a Quality-by-Design (QbD) approach for successful commercialization.[30]

6.5 SUBA™ technology: SUBA™ technology is a patented technology of Mayne Pharma, USA. Technology is based on solid dispersion via spray drying process. This technique improves the aqueous solubility or dissolution rate of poorly water-soluble drugs candidates and converts it in amorphous form as compared to crystalline forms. This technology ultimately enhances the bioavailability of poorly soluble drugs and reduced intra or inters subject patient variability. The novel SUBATM technology is approved in US, Australia, Europe and South American countries as a brand name of TOLSURA® in the US and LOZANOC® in Australia for poorly soluble anti-fungal drug itraconazole.[37]

7. Ultimate Advantages of Solid dispersion: Solid Dispersion enhances the dissolution rate and bioavailability of poorly soluble drugs due to following reasons:[18,24,32,33,37]

- ✓ Production of Amorphous form of API's in place of Crystalline compounds,
- ✓ Overall reduction of particle size of API's to its micro or molecular level,
- ✓ Hydrophilic carriers improve the wettability of API's.
- ✓ Higher porosity of formulation.

There are numerous analytical and instrumental methods to characterize the solid dispersion and distinguish amorphousor crystalline nature of materials. Differential Scanning Calorimtry (DSC), Modulated Differential Scanning Calorimetry (MDSC) and powder X-ray diffraction (PXRD) are prominently characterized the crystalline state and degree of crystallinity of molecules or API's. Fourier Transformed Infrared spectroscopy (FTIR) and Thermal Gravimetric Analysis (TGA)characterize chemical interactions of molecules with carrier. The surface morphology, qualitative characterization of crystallinity of solid dispersion is characterized by microscopy like optical microscopy, scanning electron microscopy (SEM) and transmission electron microscopy (TEM).*In-vitro* dissolution study is the most prominent method to predict *In-vivo* performance of solid dispersion. A combination of several methodsis required to characterize the solid dispersion toprovide sufficient information regarding the physical nature of solid dispersion systems in place of one single method. Table 10 highlights differentmethodsof characterization and various available approaches.[18,37,54-57]

Table 10. Methods of characterization of solid dispersion

S. No.	Characteristics of Solid Dispersion	Instrumental Methods
1.	Drug-Polymer/Carrier Interaction Study	Differential Scanning Calorimetry (DSC) Fourier Transform Infrared Spectroscopy (FTIR) Nuclear Magnetic Resonance Spectroscopy
2.	Physical State Study	Differential Scanning Calorimetry (DSC) Powder X-ray diffraction (PXRD)
3.	Microscopic Study	Optical Microscopy Scanning Electron Microscopy (SEM)
4.	Structural Study	Fourier Transform Infrared Spectroscopy (FTIR)

		Nuclear Magnetic Resonance Spectroscopy Raman Spectroscopy
5.	Intrinsic Solubility or Dissolution Study	*In-Vitro* Dissolution Apparatus

8. Solid Dispersion Characterization Techniques:

8.1 Theromoanalytical methods: Theromoanalytical methods examine the characteristic of the system as a function of temperature. Among various methods, DSC is the most highly regarded method. DSC enables the quantitative detection of all process, in which energy is consumed or produced (i.e. endothermic and exothermic phase transformation). The usual method of measurement is to heat the reference sample and test samples in such a way that the temperature of the two samples is kept identical.

If an energy-requiring phase transition occurs in the test sample, extra heat is consumed by the sample so that its temperature rises at the same rate as in the reference sample. The additional heat consumed is recorded and used to quantify the energy of phase transition. Exothermic transition, such as conversion of a polymorph to a more stable polymorph, can also be detected by this method. Amorphous form of drug is characterized by disappearance of melting peak in the DSC, which indicates that the drug is present in acrystalline form.

Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However, crystallinity of fewer than 2% cannot generally be detected with DSC. DSC is used to understand the process like glass transition, crystallization, polymorphic transition and miscibility of drug-polymer which is occurred in the solid dispersion at a molecular level.[30,35,36,38,40,41,55,57]

Differential Thermal analysis (DTA) method is used extensively to construct phase diagram of a number of binary systems. This technique is especially valuable in detecting the presence of a small amount of eutectic in the mixture. This technique identify the Glass Transition Temperature (Tg), Crystallization Temperature (Tc), Melting Temperature (Tm) and as an indication of the dissolution performance. Technique also potentiate ageing problems of solid dispersions.[36,38,41]

The polymorphism and morphology of solid dispersions can easily identify by Polarizing microscope. The fine particles of crystallization in the glass PVP matrix can be readily detected by the polarizing microscope.[37,58]

Zone melting method has been primarily used for ultra-purification of metals, inorganic and organic compounds. This technique is especially valuable in the determination of the exact chemical composition of eutectic and soild-soild solubility. This method is limited to compounds with high thermal stability and low volatility.[18,37]

Apart from these methods, other thermal methods are also being used for routine analysis in the pharmaceutical industry such as dynamic mechanical analysis and isothermal microcalorimetry method.[37,58]

8.2 Powder X-ray diffraction methods: Powder X-ray diffraction method is based on the detection of interference bands upon exposing the sample to a beam of X-ray. A characteristics fingerprint region in the diffraction pattern reflects crystallinity in the sample. Crystallinity in the drug can be separately identified owing to specificity of the fingerprint. The crystalline material gives characteristics diffraction peaks while the amorphous material gives a wide peak.[59]

Therefore, it is possible with X-ray diffraction to differentiate between solid solution, in which it is at least partly present in the crystalline forms, regardless of whether the carrier is amorphous or crystalline. However, X-ray diffraction cannot characterize crystallinity of under 5-10%.[58] The recent advances in X-ray diffraction instrument is

equipped with variable temperature or humidity control to provide an insight into molecular behavior of amorphous drugs in solid dispersion under stressed conditions.[30,36,38,40-42,55-59]

8.3 Infrared spectroscopy: IR spectroscopy identifies structural changes and lack of crystal structure in a molecule. Therefore, it is necessary to detect peaks which are sensitive in the IR spectrum to judge crystalline changes.

Fourier transform-Infrared Imaging (FT-IR) of solid dispersion provides information about the concentration of a specific compound and its morphology and chemical structure. This is particularly important in the case of drugs, which may have a complex morphology or exhibit polymorphic changes upon contact with the dissolution medium. Therefore, FTIR imaging offers a unique method of analyzing the dissolution of drug and its molecular structure as a function of time during dissolution. This technique is less sensitive in presence of moisture in sample.[30,36,40-42,60,62]

8.4 Dissolution rate method: This method compares the dissolution rate of the solid dispersion with API's (pure compounds) or their physical mixture with carrier, either in powder or dosage form. Drug dissolution from solid dispersion depends on the technology employed to prepare the dispersion, and properties of carrier used. Higher dissolution rates of the solid dispersion than corresponding physical mixtures indicates the occurrence of solid-state changes during the formation of the solid dispersion. The technique is simple to perform, except that in some binary systems, where the tablet surface may not remain constant due to the leaching of particles into the dissolution medium.[30,36,40,42,55,60,62]

8.5 Thermodynamic method: The phase diagram of eutectic and solid solution system can be constructing on the basis of some thermodynamic parameters. Knowledge of heat of fusion, entropy and partial pressure at various compositions, enables to determine the solubility gap below the solid-liquid equilibrium temperature.[58]

8.6 Microscopy method:

8.6.1 Hot stage microscopy: It is an oldest technique to study phase transition in a crystal. During microscopic study, temperature is varied which provides information about melting, recrystallization and solid-state transformation. Evolution of gas or liquid from crystal lattices can be easily observed by Hot stage microscopy.[37,55]

8.6.2 Scanning electron microscopy (SEM): SEM is often used to get primary information of the dispersed particle size systems, morphology, and surface characteristics and to detect amorphous and crystalline structures. Additionally, SEM with image processor can provide information about shape and granulometric properties of powdered sample. The application of electron microscopy techniques is however limited to chemicals with high atomic numbers.[30,36,37,40,42,60]

8.6.3 Transmission electron microscopy: This technique is used to detect crystalline substance in amorphous solid dispersion to generate both real space picture and electron diffraction patterns. Technique has self-limitation of tedious sample preparation and damage of sample by electron beam.[37,55,61]

9. Pharmaceutical Application of Solid Dispersion Techniques:

- SolubilityEnhancement of drug by moleculardispersion of the drug in the carrier, or ultimately enhancement of absorption & bioavailability of drug,[13,27,33,35]
- Fast or rapid dissolution rate,[15,16,28]
- Easy toformulateanimmediate/fast/ controlled/ delayed/ sustained release productby the application of selective carriers,[22,27,48]
- Conversion of potent Liquid drug into solid state,[51]
- Stabilization of unstable drug and protect from its decomposition,[32]
- The bitter or unpleased odor of drug can be easily masked by Solid Dispersion techniques using insoluble matrices,[27]

- Excellent Uniformity of content for potent drugs in the dosage forms,[29]
- Improve wettability of drug using carriers,[25]
- Excellent content uniformity,[39]
- Applicable for potent drug,[28,39]
- Dose of drug can be reduced by increasing solubility, absorption and ultimately improved bioavailability,[35]
- Avoidance of polymorphic changes and thereby overcoming bioavailability problems,[39]
- Protection of drug against decomposition by saliva[28,39,54]and
- Two poorly soluble drugs can be easily formulated when they have Eutectic property.[63]

Solid dispersion has vast potential in pharmaceutical industry, some commercialized products are reported in different literatures (Table 11).[24,37,55,64-80]

Table 11. Some of the approved marketed product based on Solid Dispersion Technology

S. No.	API	API Category	SD Method	Polymer/ Carrier	Manufacturer	Brand name	Dosage form	Regulatory Agency/ Approval Year
1	Duloxetine	Antidepression	Physical-Kneading	HPMCAS	Eli Lilly	Cymbalta®	Capsule	FDA-2004
2	Etravirine	AIDS	Melting - HME	Hydrocypropyl methyl cellulose	J & J	Intelence®	Tablets	FDA/EMA-2008
3	Etravirine	AIDS	Solvent Method - Spray drying		Tibotec	Intelence®	Tablets	FDA-2008
4	Everollimus	Organ transplantation	Co-precipitation		Novartis	Certican®	Tablets	FDA-2010
5	Everollimus	Immunosuppressant	Solvent Method - Spray drying		Novartis	Votubia®	Tablets	FDA-2010
6	Fenofibrate	Hyperlipidemia	Melting+Solvent-Spray melt	Poloxomer 188	Santorus	Fenoglide®	Tablets	FDA-2010
7	Griseofulvin	Antifungal	Melting - HME	PEG6000	Pedinol	Gria-PEG®	Tablets	FDA-1982
8	Itraconazole	Antifungal	Fluid bed layering	Hydrocypropyl methyl cellulose	Janssen Pharma	Sporanox®	Capsule	FDA-1992
9	Itraconazole	Onychomycosis	Melting - HME		Merz	Onmel®	Tablets	FDA-2010
10	Itraconazole	Antifungal	Solvent Method - Spray drying	HPMCP	Mayne	Lozanoc®	Capsule	NA
11	Ivacaftor	Cysticfibrosis		Hydrocypropyl methyl cellulose	Vertex	Kalydeco®	Tablets	FDA/EMA-2012
12	Ivacaftor	Cystic fibrosis		HPMCAS	Vertex Pharm.	Orkambi®	Tablets	FDA-2015
13	Metformine HCl	Antidiabetic	Melting - HME	PEG6000	Novartis	Galvusmet®	Tablets	EMA-2007
14	Nabilone	Anticancer	Solvent Method	Povidone	Valeant	Cesamet®	Capsule	FDA-1985
15	Nilvadipine	Antihypertensive	Solvent Method - Spray drying	Hydrocypropyl methyl cellulose	Fujjsawa	Nivadil®	Tablets	NA
16	Posaconazole	Antifungal	Melting - HME	HPMCAS	Merck	Noxafil®	Tablets	FDA-2013
17	Ritonavir	AIDS		Povidone	Abb Vie	Kaletra®	Tablets	EMA-2001
18	Ritonavir	AIDS			Abbvie	Norvir®	Tablets	EMA-2009
19	Rosuvastatin	Antihyperlipidemic	Solvent Method - Spray drying	Hydrocypropyl methyl cellulose	Astra Zeneca	Crestor®	Tablets	FDA-2002,EMA-2004
20	Tacrolimus	Organ transplantation	Physical-Kneading		Astellas	Prograf®	Capsule	FDA-1994
21	Tacrolimus	Organ transplantation	Wet granulation		Astellas	Advagraf®	Capsule	FDA-2012
22	Telaprevir	Hepatitis	Spray drying	HPMCAS	Vertex	Incivek®	Tablets	FDA/EMA-2011
23	Tolvaptan	Hyponatremia	Physical-Kneading	NA	Otsuka	Samsca®	Tablets	FDA/EMA-2009
24	Troglitazone	Antidiabetic	Melting - HME	Hydrocypropyl methyl cellulose	Pfizer	Rezulin®	Tablets	FDA-1997
25	Vemurafenib	AntiCancer	Co-precipitation	HPMCAS	Roche	Zelboraf®	Tablets	FDA-2011
26	Verapamil	Antihypertensive	Melting - HME	HPMC/HPC	Abbot	Isoptin SR ®	Tablets	FDA-1987
27	Vildaglaptin	Antidiabetic		Hydrocypropyl cellulose	Novartis	Eucreas®	Tablets	EMA-2007

10. Conclusion: Most of the newly discovered chemical entities are poorly water-soluble. They have a critical effect on their solubility, dissolution, bioavailability and therapeutic potential. The wide ranges of solubility enhancement approaches are available, which can play a significant role in aqueous solubility, dissolution properties and content uniformity of poorly soluble drugs. Out of these approaches, Solid Dispersion concept is very versatile for solubility enhancement in comparison to other solubility enhancement techniques. Hence, solid

dispersion successfully enhances solubility of poorly aqueous soluble drug, stability of unstable drug and thereby bioavailability by either dispersion of drug at molecular level or production of amorphous forms of drug.

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