

## SOLID DISPERSION - A NOVEL APPROACH FOR BIOAVAILABILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS IN SOLID ORAL DOSAGE FORMS

PU RNACHANDRA REDDY GUNTAKA\*, SRINIVAS LANKALAPALLI

Department of Pharmaceutics, GITAM Institute of Pharmacy, GITAM University, Rushikonda, Visakhapatnam, Andhra Pradesh, India.  
 Email: gpreddy86@gmail.com

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### ABSTRACT

Enhancement of the bioavailability of poorly water-soluble drugs is a challenging task in drug development. Currently 40% of new chemical entities are discovered as poorly water-soluble drugs. Solid dispersion is one of the best technology for improving solubility, dissolution rate, and bioavailability. Solid dispersion techniques are more useful for enhancing drug solubility for a combination of drug and inert carrier to improve wettability, reduced particle size, and converting amorphous particles. This article reviews various advantages, methods of solid dispersions, carriers used in solid dispersion, characterization, and marketed products.

**Keywords:** Bioavailability, Solubility, Dissolution, Carrier, Polymorphism.

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### INTRODUCTION

Oral drug delivery is simplest, most popular, and easy route of the administration of drugs. Recently, more than 40% of active new chemical entities are identified as poorly water-soluble drugs [1,2]. After administration drug orally, it disintegrates in gastric fluids and then solubility of drug in gastric and/or intestinal fluids and then permeability takes place in the membrane of gastrointestinal track, and it reaches systemic circulation. Hence, poorly aqueous soluble drugs have critical to exhibit dissolution rate [3].

Based on the biopharmaceutical classification system (BCS), Class II and Class IV drugs have low aqueous solubility [4].

Noyes-Whitney equation gives some idea about the dissolution rate of poorly soluble compounds which might be improved to minimize the limitations of oral availability [5].

$$Dc/Dt = AD (C_s - C)/h$$

Where Dc/Dt is dissolution rate,  
 A is dissolution surface area,  
 D is compound diffusion coefficient,  
 C<sub>s</sub> is the solubility of compound,  
 C is concentration of drug in time t,  
 h is thickness of diffusion layer in dissolving compound.

Solid dispersion has been the most efficient technique to improve the solubility, dissolution rate, and oral absorption of poorly aqueous soluble drugs [6].

Solid dispersion is defined as a dispersion of one (or) more active ingredients in inert carrier at solid state preparation using various solid dispersion techniques [7].

The mechanism to enhance solubility by solid dispersion technique involves complete removal of dry crystallinity of poorly soluble compound in a inert carrier. Prepared solid dispersion material is exposed to aqueous media; the carrier dissolves in media and the drug is releases as fine colloidal particles. This will increases the surface area of drug particles and improve dissolution rate [8]. Drug in soluble hydrophilic carrier improves the dissolution rate by reducing

particle size and increasing the particle porosity. The drug converts into crystalline form to amorphous state and improves wettability and dissolution of poorly water-soluble drugs. For better dissolution rate, purpose surfactant has been included. Surfactants are useful for better dissolution rate purpose. Surfactants are also helpful to avoid recrystallization and enhances potentiality of their solubility [9].

### ADVANTAGES OF SOLID DISPERSION

#### Reduced particle size by increased surface area

Particle size is majorly impact on dissolution rate, especially low soluble drugs. Due to reduced particle size of drug, it may lead to increase in surface area and contact of more surface area to dissolution media. Hence, it results in more dissolution rate.

#### Improved wettability of drug particles

Due to increase wettability of drug particles leads to improve solubility of drug in dissolution media. The use of carriers with or without surface active agents increases drug wettability. Carriers enhance drug solubility in dissolution media due to increased wettability of drug particles.

#### Particles with high porosity

By use of solid dispersion technique, The carriers are having high degree of porosity. carriers are useful to increases in porosity of drug particles which results improves solubility. For example, hypromellose and some of polymers have a high degree of porosity in nature. Hence, it enhances the solubility of drug in dissolution media and it leads to high dissolution rate compared to initial drug particles.

#### Drug particles polymorphic state

Polymorphic form of drug particles plays a major role in drug solubility in dissolution media. Crystalline nature of drug particles has less solubility comparative to amorphous drug particles. Crystalline polymorphic form of drug particles requires more energy to break the crystalline lattice, whereas amorphous drug particles require less energy to break the particles. Using additional surface active agents, it will more useful for the enhancement of solubility in dissolution media.

#### Solid dispersion

Based on solid-state structure and carriers, solid dispersions are classified into different ways. Solid dispersion was performed using

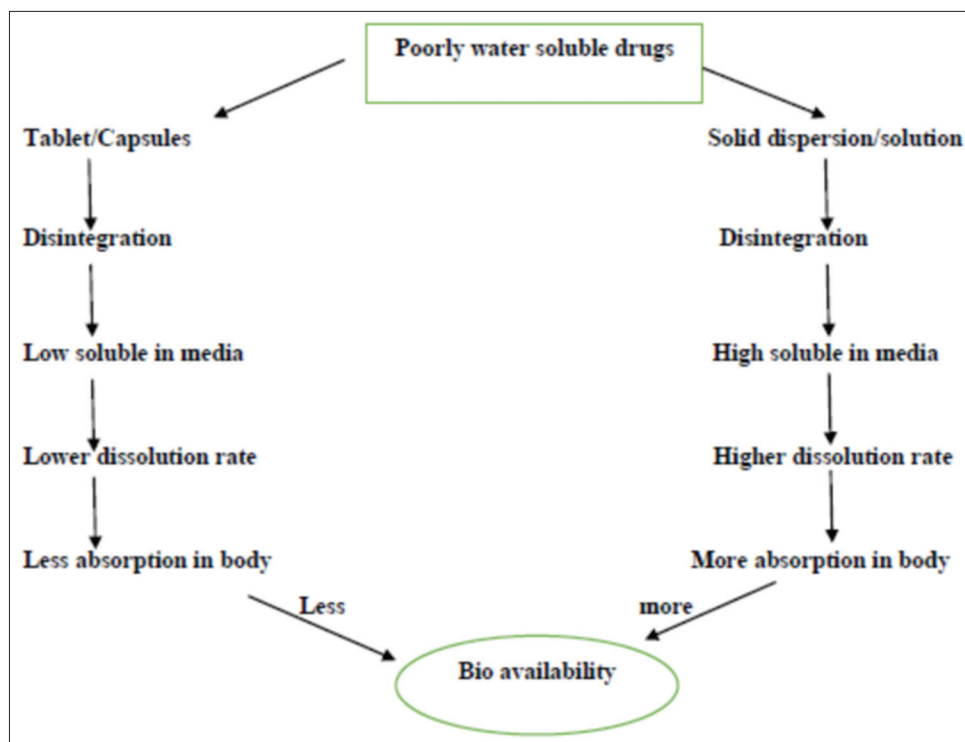


Fig. 1: Schematic representation of aqueous soluble drug

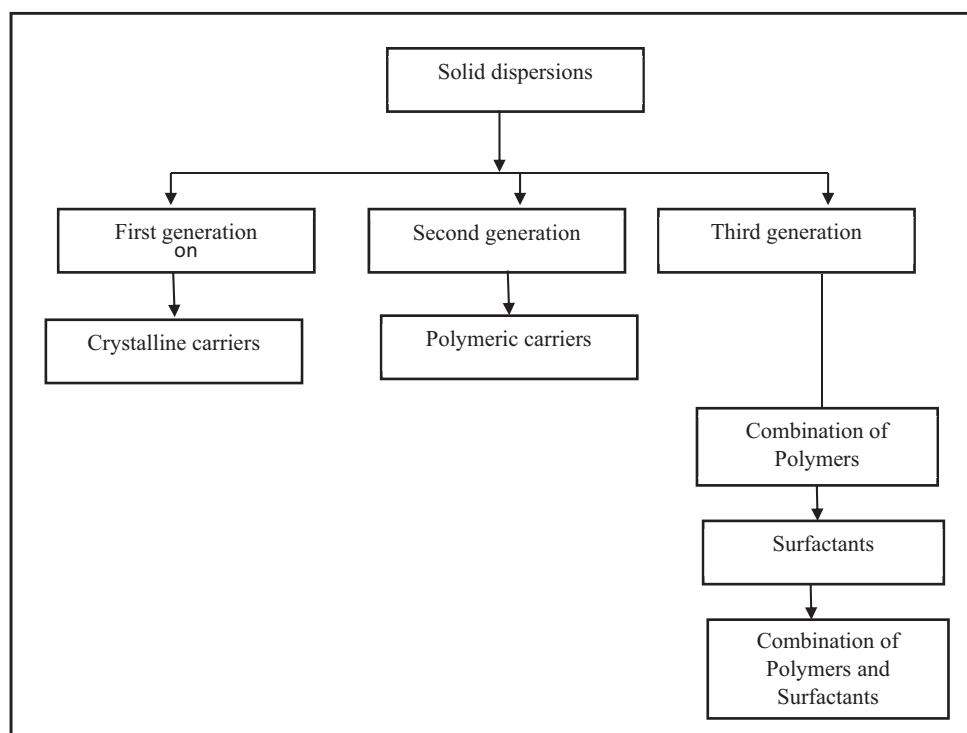


Fig. 2: Classification of solid dispersion on the basis of carrier used

different methods based on molecular structure and nature. To enhance the solubility of active pharmaceutical ingredient (API), various preparations of solid dispersions were used based on principle and mechanism. Riegelman and Chiou classified solid dispersions into the following six representative types: Amorphous precipitations in a crystalline carrier, simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, compound or complex formation, and combinations of the previous five types. Given below is the

classification of solid dispersion on the basis of carrier used and solid structure [10].

#### First generation

In the first generation, solid dispersions were developed by crystalline carriers. In general, the crystalline carriers such as sugar and urea are used. The crystalline carriers are thermodynamically more stable. But the disadvantage is some of the drugs are not suitable with

crystalline carriers its cannot release the drug in dissolution media because of crystalline nature of API. In this crystalline carriers unable to convert drug nature from crystalline to amorphous. By presence of crystalline nature of drug it leads to low solubility and bio availability [11,12].

### Second generation

The second-generation solid dispersions are used as amorphous carriers instead of crystalline carriers like polymers. When compared to the first generation, second-generation carriers are more helpful by converting drug in amorphous nature, which was more useful for drug solubility in dissolution media. Different polymers such as polyvinylpyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), polyethylene glycol (PEG), and HPMC. Using these polymers, the drug nature was converted and improves in bioavailability [13,14].

### Third generation

Nowadays, the third-generation solid dispersions are used continuously for improving better solubility purpose. In this third generation, both the combination of surfactant and polymers and combination of polymers were used. It will more helpful for converting drug crystalline nature to amorphous nature and improved solubility in dissolution media because of surfactant. In this third generation solid dispersion technique is most effective to enhance solubility and bio availability of poorly water soluble drugs [15,16].

### Preparation of solid dispersions

Many methods are used for the preparation of solid dispersion systems, and some of them are enlisted as follows:

1. Spray drying
2. Hot melt extrusion method
3. Solvent evaporation method
4. Fusion/melting method
5. Melting solvent method
6. Lyophilization techniques
7. Melt agglomeration process
8. Electrospinning method
9. Supercritical fluid technology.

#### Spray drying

Spray drying technique is one of the most effective and commonly used solid dispersion methods. It is a single step, convenient, and easy to reproducible process. Mainly principle involved in spray dry technique is continuous transformation of converting material from liquid state to solid state using a heat drying chamber. In this process drug, polymer, sometimes surfactants, dissolves in solvent and continuous spraying in heating chamber where solvent is evaporated and converted into solid state [17].

In this drying chamber, solvent is sprayed using atomization air. The solvent is converted into fine droplets due to atomization air and converts solid particles in drying chamber.

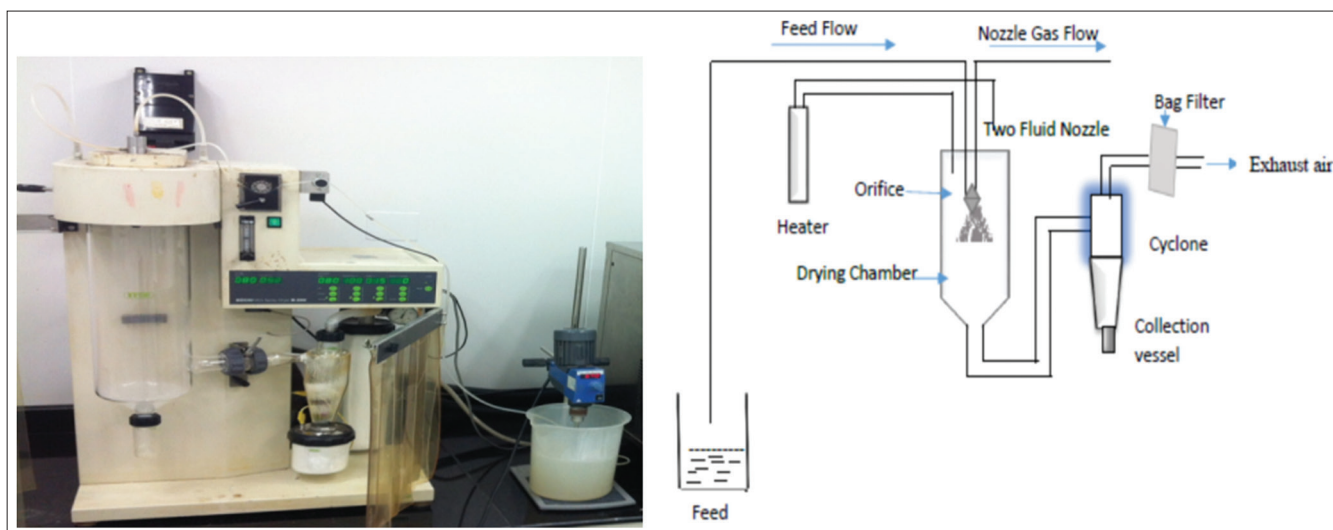


Fig. 3: Schematic diagram of spray dryer

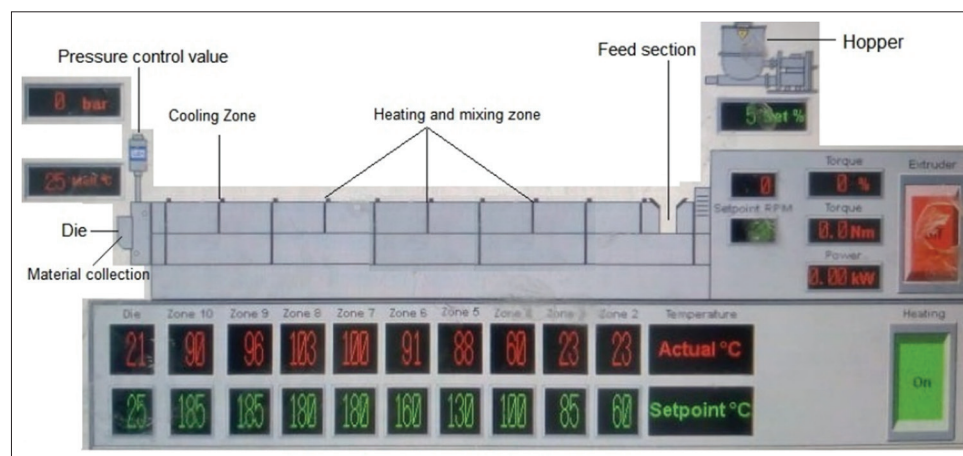


Fig. 4: Schematic diagram of hot melt extrusion

In this technique, drug and inert carriers were completely dissolved in suitable solvent. The solvent used was single solvent or mixture of solvents based on the solubility of drug and inert carriers. Due to the solubility of drug and inert carriers, drug particles converted its crystalline nature to amorphous nature and it improves the solubility and bioavailability.

Polymers generally used as PVP, copovidone, HPMC, hydroxy propyl cellulose, and Soluplus surfactants as sodium lauryl sulfate, docusate sodium, and polysorbates. The drying chamber temperature was selected based on boiling point of solvents used. Different solvents are having various boiling points [18].

Solvents	Boiling point
Water	100°C

Acetone	56°C
Isopropyl alcohol	83°C
Ethanol	78°C
Dichloromethane	40°C
Methanol	65°C

#### Hot melt extrusion method

Recently, hot melt extrusion method is more popular due to most of the formulation focusing in this technique to improve the solubility of poorly soluble drugs. The advantage of hot melt extrusion is less process time, effective technique of converting crystalline polymorphic form to amorphous polymorphic form. The main selection of hot melt extrusion technique rather than spray drying technique due to very less solubility of drug in solvent will require more solvent for dissolving drug in media. In this technique, there was no need of solvent. Hence,

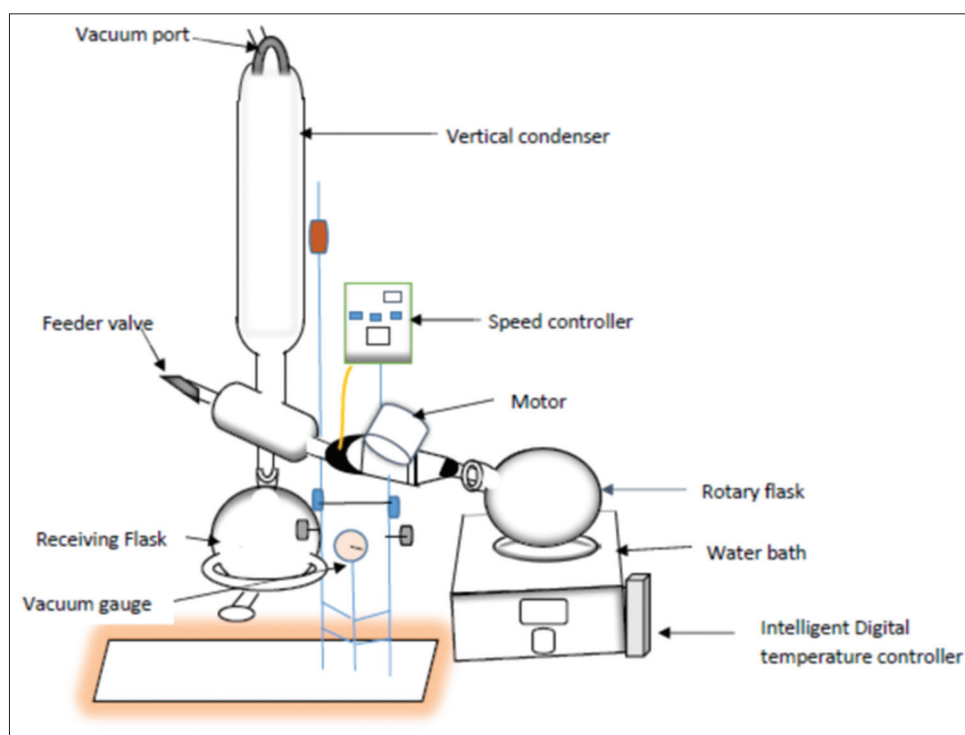


Fig. 5: Schematic diagram of solvent evaporation technique

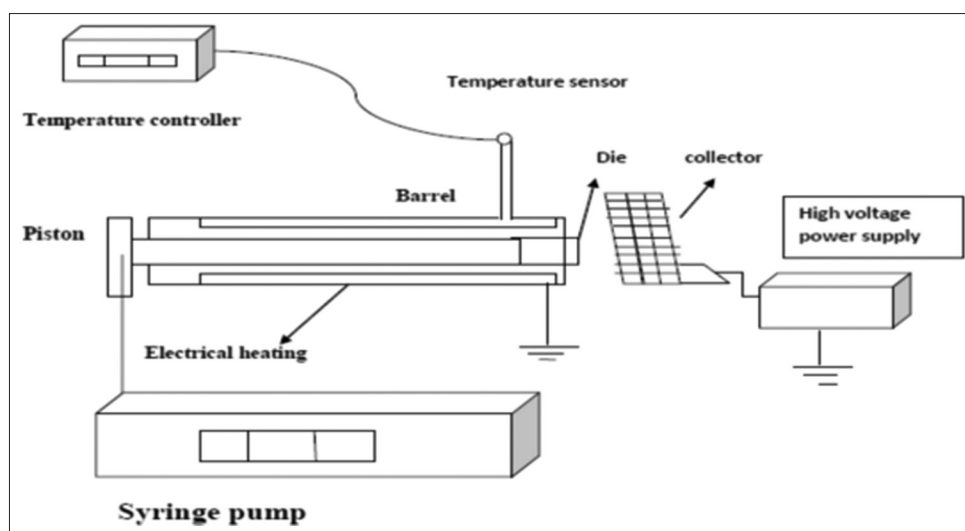


Fig. 6: Schematic diagram of melting solvent technique

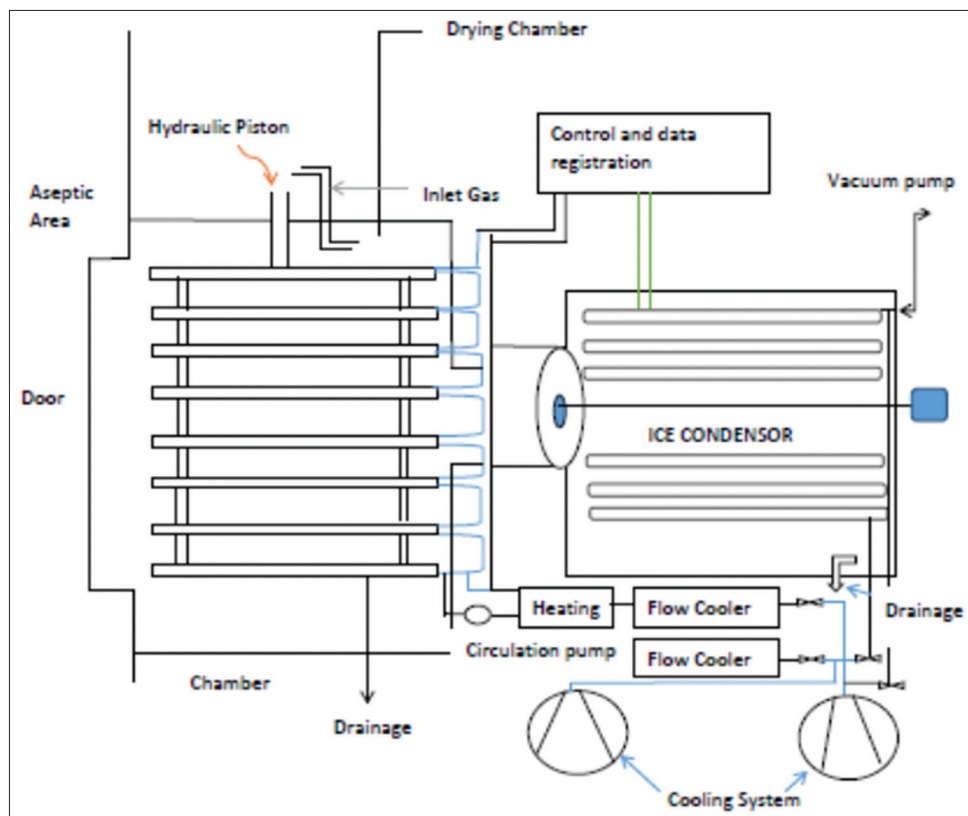


Fig. 7: Schematic diagram of lyophilizer technique

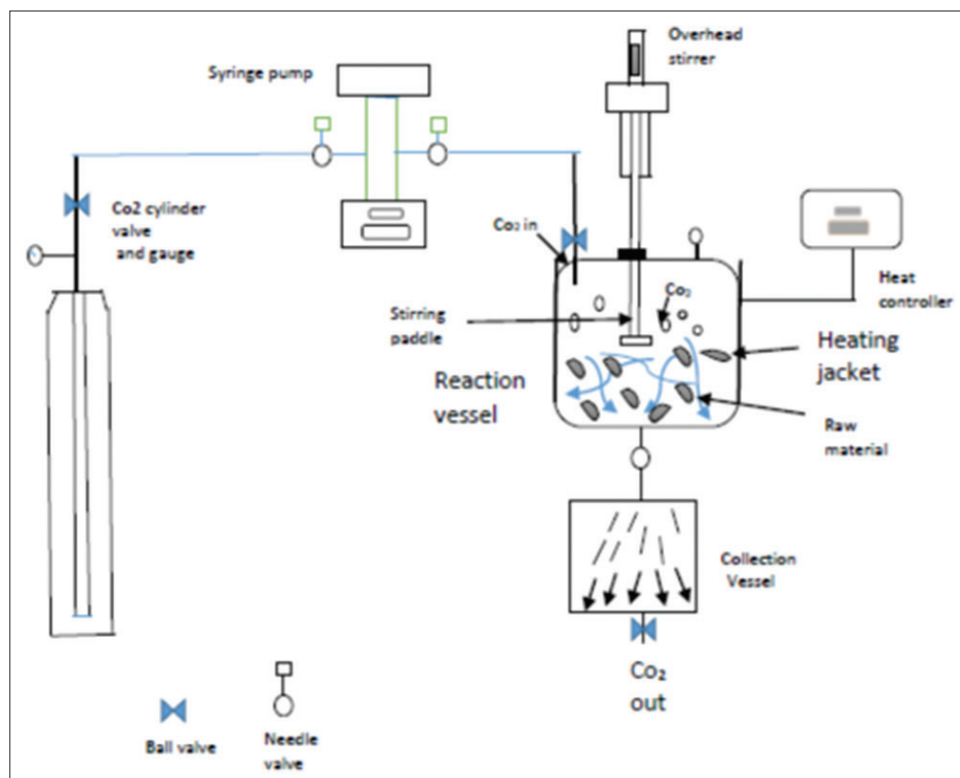


Fig. 8: Schematic diagram of supercritical fluid technique

depending on physicochemical property of drug, molecular hot melt technique was selected [19].

Hot melt extrusion is a continuous process to apply heat and pressure to melt a drug and polymer mixture in different heating chambers.

Finally, the melted mixture reaches cooling chamber and it converts into solid flakes. Melting reaches up to glass transition temperature ( $T_g$ ) of polymeric material. The selection of polymers depending on drug melting point [20].

Ingredients	Melting temperature
Co povidone	140°C
Polyvinylpyrrolidone	150°C
Hypromellose	190–200°C
Soluplus	150°C
Polyethylene glycol	37–48°C

#### Solvent evaporation method

In general, rotavapor is used for solvent evaporation method. In this method, drug and polymer dissolve in common organic solvent and the solvent is evaporated at low temperature. Then, the resulting mixture is milled through suitable screens. Some of the products are not suitable in this technique because only single solvent is utilized in this process. If drug is soluble in one solvent and polymer is dissolved in another solvent at the time of evaporation, solvents are evaporated based on boiling point, so drug or polymer solidified quickly based on the solvent used. It will lead to not complete polymorphic conversion occurs. So finally creates a low soluble and low dissolution rate. Hence, drug and polymer dissolve in single solvent only. The selection of polymer is based on drug nature and solubility of drug in organic solvent. In general, solvents used ethanol, acetone, isopropyl alcohol, and dichloromethane. [21,22].

#### Fusion/melting method

In this process melting of drug with inert carrier at particular temperature, it produces the waxy type material by combined of drug particles with inert carrier. Then, waxy material placed in cooling chamber and milling through suitable screen. The main disadvantage is drugs which are having temperature sensitive or low melting point not suitable in this technology. In general, melt granulation through rapid mixer granulation is used in this method. In this process, heat is produced continuously in outside of the chamber and inside of chamber drug, and the drug and carrier rapid mixing takes place at certain time, it converts waxy type material. Later, cool water is circulated outside of chamber, it converts solid mass, and then, it places to milling and mixing [23,24].

#### Melting solvent method

Melting solvent method is a combination of both processes at a time, i.e., melting and solvent evaporation method. In this technology, drug is dissolved in suitable solvent after getting clear solution directly incorporated into melt of suitable carrier. Then, continuous low heat circulated in outside until the complete solvent is evaporated. The resulting residue is the combination of drug and inert carrier then solidified it properly [25]. The solid material is milled with suitable screen and mixed with other excipients. The main advantage of this method is drugs which are having low melting and high temperature-sensitive drugs which are suitable in this method [26,27].

#### Lyophilization techniques

It is also called as freeze-drying in this process drug, and inert carrier dissolves in common solvent. The solution is frozen and sublimation under vacuum. The frozen state material is placed in low air pressure and it converts in glassy-like structure. The advantage of this process is minimal thermal stress and risk of phase separation is low. It is a technology that the drug substance maintains quality and stable [28,29].

**Table 1: Solubility criteria as per USP and BP descriptive term part of solvent required per part of solute**

Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10,000 and over

#### Melt agglomeration process

In this technology, drug and polymer or binder is placed in continuous mixing chamber. Then generates heat based on the melting point of drug. then drug and inert carrier mixing together and formulates a agglomerates. In this process find particles are melted together and forms a agglomerates. By enhancing dissolution rates use surfactants also. In this method resulting flowable material obtains to increases flow properties [30,31].

#### Electrospinning method

This is a nanotechnology majorly used for polymer industry. In this method, a liquid stream of drug and polymer solution involves into potential between 5 and 30 Kv. When electric forces overcome to surface tension of drug and polymer solution at air interface, it involves the strong electrostatic field over a polymer solution to form a submicron diameter fibers [32]. The fiber diameter completely depends on dielectric constant, surface tension, electric field strength, and feeding rate [33,34].

#### Supercritical fluid (SCF) technology

Using SCF technology to prepare solvent free dosage forms. It is a single fluid phase above the critical temperature and pressure. Carbon dioxide is commonly used for supercritical fluid as chemically inert nature, non-flammable, and non-toxic. In this process, drug particles soluble with supercritical fluid and then recrystallization with reduced particle size as per requirement. The carbon dioxide is used for anti-solvent purpose [35,36].

#### CARRIERS USED IN SOLID DISPERSION [37]

##### PVP

PVP is used in a different pharmaceutical formulation mainly solid oral dosage forms. It is a fine, odorless, white to creamy white-colored hygroscopic material. It is available in different grades divided in its K-value. Based on molecular weight, K value available. K-value is from 12 to 120 having molecular weight of 2500–3,000,000. Melting point of PVP is 150°C. The solubility is freely soluble in water, acids, chloroform, methanol, and ethanol. The viscosity of aqueous solubility depends on its molecular weight and concentration used [38,39].

##### Copovidone

Copovidone is commonly used as a carrier of spray dry technology due to its low viscosity and better binding property. The description of copovidone is a white to yellowish white color, and it is slightly have odor component. The melting point of copovidone is 140°C and it is a stable component. The T<sub>g</sub> of copovidone is 106°C. Due to low-temperature glass transition nature, it is used as hot melt extrusion technology also. The solubility of copovidone is freely soluble in water, glycerol, PEG 400, and ethanol. The viscosity is <10 mPas at a concentration <10% [40].

##### HPMC

It is also called as hypromellose. It is widely used in many pharmaceutical dosage forms in different ways due to its viscosity ranges. The description of hypromellose is white to creamy white fibrous material of odorless, and it is hygroscopic in nature. It is available in various viscosity ranges of very low viscosity 3 mPas to high viscous range of 200,000 mPas. The melting point is about 190–200°C and T<sub>g</sub> is 170–180°C. the solubility of hypromellose is soluble in cool water and n hot water, ethanol, ether, and dichloromethane. Hypromellose is repeatedly used as a carrier in hot melt technology for conversion of crystalline polymorphic form to amorphous polymorphous form which was useful for improving solubility [41,42].

##### Hydroxypropyl cellulose (HPC)

HPC is an cellulose where some of the hydroxyl groups of the cellulose have hydroxyl propylated forming groups. It is a white to slightly yellow-colored odorless powder. HPC is commonly available in different grades depending on its viscosity. The viscosity ranges from 50,000 to 1,250,000 mPas. It is

a stable molecular having melting point 130°C. The solubility of HPC is freely soluble in water, soluble 1 in 10 parts dichloromethane, and 1 in 2.5 parts in ethanol. The pH of HPC is 5.0–8.0 [43].

### PEG

PEG is a hydrophilic substance. It is available in different grades based on different molecular weights of PEG 200–8000 having molecular weights 190–9000. It is available in both liquid form and solid forms up to grade PEG 400 which are liquid materials. The description of PEG liquid grades is clear slightly yellow color and solid PEG is off-white in color. It is having very low melting point of 37–48°C. Due to its very low melting, nature may have stability problems. The solubility of PEG is freely soluble in water, glycerine, acetone, and alcohol [44,45].

### Soluplus

Soluplus is a graft copolymer it contains combination of polyvinyl caprolactam, polyvinyl acetate, and PEG. The description of Soluplus is white to slightly yellowish granules. It is a hydrophilic carrier polymer majorly designed for poorly soluble drugs. The advantage of Soluplus improves solubilization property and enhances bioavailability. Due to its excellent extrudability, it is mainly used as a hot melt extrusion process to improve solubility. The solubility of Soluplus is freely soluble in water, acetone (up to 50%), and methanol (up to 45%). The T<sub>g</sub> is 70°C.

### Carboxymethyl cellulose

The carboxymethyl cellulose is a stable, hygroscopic substance and description is white to almost white odorless granular powder. It is available in different viscosities of low to high (10–12,000). It is practically insoluble in water and melting point also high 220°C. It has both binder and disintegrate properties [46,47].

### Eudragits

Eudragits are regularly used in pharmaceutical solid oral dosage forms containing synthetic cationic and anionic polymers. It is also called as polymethacrylates. It is available as different stages (dispersion, solid, and organic solutions) and different grades are having different applications based on pH dependent and pH independent. Typically, the molecular weight of polymer is above 100,000. Eudragit E is soluble in gastric fluids about pH 5, Eudragit L is soluble in above 6, and Eudragit S are soluble in above pH 7. Eudragit RL are forms water-insoluble film and are more permeable than those of Eudragit RS. The solubility of eudragits is a mixture of organic solvents isopropyl alcohol, acetone, and water [48].

### Hypromellose acetate succinate

Hypromellose acetate succinate is a white to off-white powder and available in several grades according to the pH at which polymer dissolves (low - L, medium - M, and high - H), the molecular weight is approximately 55,000–93,000 Da. It is a solubility-enhancing agent through solid dispersion and is insoluble in gastric fluid but will swell and dissolve rapidly in the upper intestine. The T<sub>g</sub> is 113°C. The solubility is a mixture of ethanol and dichloromethane in 1:1 ratio [49].

### Hypromellose phthalate

Hypromellose phthalate is a white to slightly off-white freely flowing flakes granular odorless powder. Hypromellose phthalate is a cellulose in which some of the hydroxyl groups are replaced with methyl esters. Different types of hypromellose phthalate are commonly available with molecular weight in a range of 80,000–130,000 Da. It is a hygroscopic material having T<sub>g</sub> of 137°C and melting point of 150°C. The solubility is a mixture of acetone and methanol or ethyl alcohol 1:1 ratio [50].

### Acids

In general, acids are high soluble components and are used as pH modifiers in pharmaceutical dosage form which was useful for pH-sensitive molecules. Mainly citric acid monohydrate and tartaric acid are commonly used in the formulation. These are transparent crystalline, hygroscopic nature. The low melting point acids are converts into

soften in nature. Different grades are available based on particle size difference [51].

### Sugars

Simple sugars are named as monosaccharides which include sucrose, dextrose, glucose, and fructose. A part from this sugar alcohol is available which is called as polyols including sorbitol, mannitol, and xylitol. Sugars are high soluble hygroscopic substances. The melting point range is 160–186°C. Sugar alcohols are freely soluble non-hygroscopic substances. These are commonly used as solid oral dosage forms as a plasticizer and diluent. Compared to sugars, sugar alcohols are stable substances. The common melting range is 166–168°C. It is suitable as moisture-sensitive active ingredients due to its non-hygroscopic nature [52].

### Surfactants

Surfactants play a major role in pharmaceutical products. Surfactants are surface active agents which reduce surface tension. It improves the wettability of solid surface of drug particles it leads to improved solubility. In solid dispersion technology surfactants used for combination of polymers because it enhances solubility, dissolution rate and improves the bioavailability. It is classified into four types: Anionic, nonionic, cationic, and amphoteric surfactants [53].

#### Anionic surfactants

It dissolves in water negatively charged particles created. Sodium lauryl sulfate is anionic surfactant commonly used in formulations.

#### Cationic surfactants

It dissolves in water positive-charged particles created. Quaternary ammonium salts and amines with amide linkages are some of the examples of cationic surfactants.

#### Non-ionic surfactants

It contains hydrophilic groups. Tweens and spans are common examples of non-ionic surfactants.

#### Amphoteric surfactants

These are also called as zwitterionic surfactants and it contains both anionic and cationic centers attach to the same molecular. Examples are sodium dodecyl sulfates phospholipids.

### Characterization of solid dispersions [54-78]

1. Physical appearance
2. Drug content
3. Dissolution
4. Electron microscopy
5. X-ray powder diffraction (XRD) studies
6. Fourier transform infra red (FTIR) spectroscopy
7. Differential scanning calorimetry (DSC).

#### Physical appearance

It involves the appearance of solid dispersion by visual inspection.

#### Drug content

It is a analysis of the amount of drug present in solid dispersion. The assay method of drug is taken and dissolved in suitable solvents which ensure that freely soluble in nature and dilute it in appropriate concentration. Finally drug content measured by UV or high performance liquid chromatography (HPLC) method.

#### Dissolution

Dissolution measures the dissolve component at particular time period. The percentage of drug release at particular time period measured by basically UV or HPLC methods. The study is performed at pre-determined volume and RPM at 37±0.5°C. As per USP 7 dissolution apparatus are available. Commonly, basket or paddle apparatus is used

Table 2: Solid dispersion technology used in marketed products [79,80]

Product name/substance	Technology used	Company
UROCIK-K/Potassium citrate	Melt granulation	Mission Pharmacal Co
KALETRE/Lopinavir and Ritonavir	Hot melt extrusion	ABBVIE INC
Intelence/Etravirine	Spray drying	Janssen Research and Development
Sporanox/Itraconazole	Spray layering	Janssen Pharmaceuticals
Gris-PEG/Griseofulvin	Melt process	Valeant Pharmaceuticals
Zortress/Everolimus	Spray drying	Novartis Pharmaceuticals
Zelboraf/Vemurafenib	Coprecipitation	Hoffmann-La Roche
Kalydeco/Ivacaftor	Spray drying	Vertex Pharmaceuticals
Orkambi/Ivacaftor; Lumacaftor	Spray drying	Vertex Pharmaceuticals

for solid oral dosage forms.

USP app	Description	Dosage forms
Apparatus I	Basket	Conventional, chewable and controlled-release tablets, capsules
Apparatus II	Paddle	Conventional tablets, ODT, ER
Apparatus III	Reciprocating cylinder	CR and chewable tablets
Apparatus IV	Flow-through cell	ER, poorly soluble API formulations, microparticles, implants
Apparatus V	Paddle over disk	Transdermal
Apparatus VI	Cylinder	Transdermal
Apparatus VII	Reciprocating holder	CR (non-disintegrating oral and transdermal)

#### Scanning electron microscopy

It is used to find the images of sample by scanning to surface of material with focused beam. Electron microscopy is helpful to morphological structure of material.

#### XRD studies

Powder XRD studies play a major role for identifying polymorphic forms, i.e., crystalline or amorphous. Based on diffracted beam angles and intensities of molecular structure to particular drug components 2 theta values occurs.

#### FTIR spectroscopy

FTIR spectroscopy gives a clear picture of interaction between drug to drug and drug to excipients. It measures intensity over a narrow range of wavelengths at a time.

#### DSC

DSC is a thermoanalytical technique which measures endothermic and exothermic reactions by increasing temperature gradually. Endothermic reactions measure melting and boiling points. Exothermic reactions measure crystallization and polymerization (Table 2).

#### CONCLUSION

Solid dispersion system is extremely useful for improving solubility and dissolution rate of poorly water solubility drugs, i.e., BCS Class II and IV drugs. The various solid dispersion techniques described above are useful to improve the solubility of drug substance. Based on drug nature, the selection of solid dispersion method is required for the enhancement of bioavailability. Drug is exposed to carrier in the presence of solvent the resultant mixture which is fine colloidal particles to produce higher bioavailability. It can significantly increase porosity and wettability properties of drug. Sometimes, surfactants are also useful for better improvement of dissolution rate. For higher solubility rates, optimization of polymer and surfactant concentration is required.

#### AUTHORS' CONTRIBUTIONS

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#### CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest.

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