EXPERT OPINION

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Solid dispersions: a strategy for poorly aqueous soluble drugs and technology updates

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Introduction: Present article reviews solid dispersion (SD) technologies and other patented inventions in the area of pharmaceutical SDs, which provide stable amorphous SDs.

Areas covered: The review briefly compiles different techniques for preparing SDs, their applications, characterization of SDs, types of SDs and also elaborates the carriers used to prepare SDs. The advantages of recently introduced SD technologies such as RightSize™, closed-cycle spray drying (CSD), Lidose® are summarized. Stability-related issues like phase separation, re-crystallization and methods to curb these problems are also discussed. A patented carrier-screening tool for predicting physical stability of SDs on the basis of drug–carrier interaction is explained. Applications of SD technique in controlled drug delivery systems and cosmetics are explored. Review also summarizes the carriers such as Soluplus®, Neusilin®, Solumer™ used to prepare stable amorphous SD.

Expert opinion: Binary and ternary SDs are found to be more stable and provide better enhancement of solubility or dissolution of poorly water-soluble drugs. The use of surfactants in the carrier system of SD is a recent trend. Surfactants and polymers provide stability against re-crystallization of SDs, surfactants also improve solubility and dissolution of drug.

Keywords: bioavailability, dissolution, solid dispersion, solubility

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1. Introduction

Since decades, the poor aqueous solubility of drugs has been a big challenge for formulation scientists. Poor aqueous solubility often results in compromised bioavailability. Several methods have been employed to enhance the solubility, dissolution and bioavailability of poorly soluble drugs. Some of these methods are particle size reduction, cyclodextrin complexation, solubilization, co-solvency, solid dispersion (SD), salt formation, polymorphs, solvates or hydrates, pro-drugs, microparticulates (liposomes, microspheres, etc.). But each of these methods has some practical limitations. All drugs cannot be reduced to desired particle size, or on size reduction it is not necessary to enhance dissolution rate. Further, the micronized particles may start agglomeration or develop surface charge which leads to less active surface area and poor wettability. The particle size reduction is an energy-dependent process which may not be suitable for stress-labile (thermolabile, compaction sensitive) drugs. Cyclodextrin complexation is commonly used to enhance solubility and dissolution rate. But it involves an expensive process, excipients and even it fails some time to complex with many drugs. The solubilization and co-solvency are used for liquid formulations. The patient compliance and commercial viability of liquid formulations are low. Further, the liquid formulations are difficult to handle, storage and their shelf

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Article highlights.

- Numerous techniques are available to prepare solid dispersions (SDs).
- Binary and ternary SDs are comparatively stable.
- The surfactants and polymers are used to improve the characteristics of SDs.
- Recent SD technologies such as RightSize™, Lidose®, Suba™ and closed-cycle spray drying (CSD) have provided improved SDs.
- Carriers such as Soluplus®, Neusilin®, Solumer™ and Sylysia provide stable amorphous SDs and improve the solubility, dissolution and bioavailability.

This box summarizes key points contained in the article.

life is also less when compared with solid formulations. Salt formation has been proved to be a good option for solubility enhancement. The limitations of this method are neutral drugs, weakly acidic or basic drugs and chemical reactions to prepare suitable and stable salts. Microparticulate formulations are in recent trend for improving bioavailability of poorly soluble drugs. These formulations are difficult to scale-up with uniformity and consistency. Along with high production cost, the stability of microparticulates is of big concern. The pro-drugs have shown limited scope in bioavailability enhancement by increasing the solubility of drugs.

SDs have been proved to be one of the promising technologies to improve the solubility, dissolution and bioavailability. In SD the drug exists in molecular or amorphous or microcrystalline state. The solubility and wettability of drug is improved in amorphous state, which increases the dissolution rate of drug. Disulfiram is hardly absorbed from the cornea but its SD with polyvinylpyrrolidone (PVP) prepared by the spray drying method improves its ocular bioavailability [1]. The physical and chemical stability of fluvastatin was enhanced by making SDs of drug with different polymers like PVP, Eudragit RS100 and chitosan [2].

2. Solid dispersions

SDs can be prepared by using numerous processes and methods. Along with process diversity the wide range of carriers/polymers also strengthen the concept of SDs. In recent years, binary, ternary and quaternary SDs have been developed to improve the stability of dispersions, and also to prevent recrystallization of drug in the carrier. Apart from conventional applications, the SDs also have been explored for making controlled- or sustained-release products [3]. Madgulkar *et al.* incorporated SD in bioadhesive drug delivery system [4]. The SDs were incorporated into capsules, tablets [5], bioadhesive films [6], bioadhesive tablets [4], dry powder inhalation [7], implants [8] and inhalation therapy [9]. Most commonly, the SDs are formulated into tablets and capsules. SDs of numerous poorly soluble drugs along with carriers and method of preparation are enlisted in **Table 1**.

SDs work through various mechanisms. The mechanism depends on the type of SD, interaction between drug, carrier and other carriers used to prepare it.

- High-energy metastable state/amorphous form.
- Reduction of particle size to nearly molecular level.
- Presence of carrier prevents aggregation of drug particles.
- Carrier material also prevents crystal growth.
- Intermolecular hydrogen bonding between drug molecule and carrier.
- Wetting properties are increased.
- Co-solvent or solubilization effect of water-soluble carriers.

There are several factors which affect the characteristics of SDs. The most prominent are nature of drug [10], carrier type, drug/carrier ratio, methods and process of preparing SD, particle size of drug (solid–solid interaction) [11] and drug loading [12,13].

2.1 Types of solid dispersions

1. Simple eutectic mixtures: the drug and carrier are completely miscible at liquid state but almost insoluble in solid–solid state. Drug and carrier both exist in crystalline state.
2. Solid solutions: drug dispersed at molecular level in crystalline solid carrier.
    a. Continuous solid solutions
    b. Discontinuous solid solutions
        i. Substitutional solid solutions
        ii. Interstitial solid solutions
3. Glass solutions and suspensions: drug dissolved or suspended in glassy system. Crystalline, amorphous or molecular dispersion of drug in amorphous carrier.
4. Amorphous precipitations in a crystalline carrier: dispersion of amorphous drug in crystalline carrier.
5. Compound or complex formation

2.2 Carriers for solid dispersions

Carrier selection is a difficult process. It is based on the requirements such as highly water-soluble carriers are preferred for solubility, bioavailability and dissolution rate enhancement, and on contrary water insoluble or slowly soluble or swellable or enteric polymers are used to prepare controlled- or delayed-release formulations. The water-insoluble carriers such as porous silica also have been used to improve the solubility and dissolution. The chemical and physical compatibility of carrier(s) with drug is highly desired. The SD of hygroscopic hydrophilic carriers with hydrophobic drugs often results into re-crystallization of drug. Apart from

Table 1. Summary of SDs.

Drug candidate	Carrier	Application	Preparation method
Meloxicam	Poloxamer 188	Dissolution	Kneading
Griseofulvin	HPMC-AS/PHPMA	Provides stable amorphous form Dissolution	Spray drying
Total flavones of *Hippophae rhamnoides* L.	Poloxamer 188	Dissolution	Solvent evaporation
Itraconazole	HPMC	Wettability	Spray drying
Verapamil hydrochloride	Eudragit RLPO Kollidon® SR	Controlled release	Solvent evaporation
Lovastatin	Modified locust bean gum	Solubility	Modified solvent evaporation
Itraconazole	Eudragit E100	Dissolution	Spray drying
Aceclofenac	Sodium lauryl sulfate and alkyl polyglucosides	Dissolution	Solvent evaporation
Artemether	Mono amino glycyrrhyzinate pentahydrate	Taste masking Dissolution	Solvent evaporation
Cyclosporin A	Inulin	Dry powder inhalation	SFD
Rofecoxib	Poloxamers	Dissolution	Melting method
Ofloxacin	PEG and surfactant	High drug-loaded	Solvent evaporation
Prednisolone	PEG-6000	Dissolution	Solvent evaporation
Cyclosporin	PEG-6000	Dissolution	Solvent evaporation
Meloxicam	Gelucire 50/13	Solubility and dissolution	Spray drying
IBU	PEG 4000 and Tween 80	Fast release	Solvent evaporation and melt solvent
Sibutramine	Poloxamer HPMC and citric acid	Solubility, dissolution and bioavailability	Spray drying
Etoricoxib and celecoxib	PVP	Amorphous stabilization	Spray drying and melt granulation
Irbesartan	HPMC E5LV	Solubility, dissolution and bioavailability	Spray drying
Carvedilol	Porous silica	Wettability and physical stability of the amorphous	Solvent evaporation
Promethazine hydrochloride	Eudragit RLPO and Eudragit RS100	Controlled release	Co-evaporation Co-precipitation
Acetaminophen	Chitosan	Release slowed down	Spray drying
Nilvadipine	Polyplasdone XL-10 Metolose SM-25	Solubility Dissolution Stability	Agitation granulation
Tolbutamide	HPMC	Dissolution	4-Fluid nozzle spray drying
Salbutamol sulfate	Eudragit RS (RS) Eudragit RL (RL)	Sustained release	4-Fluid nozzle spray drying
ETZ THEO	CP	Increase ETZ release Decrease THEO rate	TSE
Meloxicam	Skimmed milk	Dissolution	Solvent evaporation
Nitrendipine	CP HPMCP	CP improves, HPMCP reduces dissolution	TSE
Indomethacin	Porous silica Non-porous	Dissolution	Spray drying
Prednisolone	Skimmed milk	Solubility and dissolution	Lyophilization
Nifedipine	PVP HPMC PHPMA	Nifedipine–PVP: rapid dissolution	Spray drying
IBU	Kollidon	Dissolution	Pulse combustion dryer system
Gliclazide	PEG-6000 Pluronic F68	Dissolution	
Docetaxel	PVP-K30 and sodium lauryl sulfate	Bioavailability	
Metformin hydrochloride	Compritol 888 ATO	Sustained release	

CP: Carbopol; ETZ: Ethenzamide; HPMC-AS: Hydroxypropyl methylcellulose acetate succinate; IBU: Ibuprofen; Na-CMC: Sodium carboxymethylcellulose; PEG: Polyethylene glycol; PEO: Polyethylene oxide; PHPMA: Poly[*N*-(2-hydroxypropyl)methacrylate]; PVP: Polyvinylpyrrolidone; SAS: Supercritical antisolvent; SD: Solid dispersion; SFD: Spray freeze drying; THEO: Theophylline; TSE: Twin screw extruder.

Table 1. Summary of SDs (continued).

Drug candidate	Carrier	Application	Preparation method
			Solvent evaporation and closed melt method
Nifedipine	Ethylcellulose and Eudragit RL	Evaluate extent of dispersion	Fusion > co-evaporation > co-precipitation
Griseofulvin, progesterone and phenindione	PVP and PHPMA	Miscibility and stability of amorphous form	Spray drying
Clopidogrel napadisilate	HPMC and colloidal	Bioavailability	Spray drying
Biochanin A	Solutol HS15 and HPMC 2910	Bioavailability	
Budesonide	Dextran	Colon delivery	
Ketoconazole	Nicotinamide	Solubility and dissolution	Melting
Irbesartan	HPMC E5LV	Solubility Dissolution Bioavailability	Spray drying
Candesartan cilexetil	PEG-6000 and Gelucire 50/13	Solubility and permeability	Melt agglomeration and solvent evaporation
Diacerein	PEG-6000	Solubility and dissolution	Melting method
Lamotrigine	Poloxamer 407	Dissolution	Melt
Itraconazole	Vitamin E TPGS	Solubility and dissolution	Microwave irradiation
Gemfibrozil	PEG-6000 and sucrose laurate	Dissolution	Melting
IBU	Mesoporous silica (MCM-41 and SBA-15 and SBA-15-LP)	Amorphous and nanocrystalline IBU	Co-spray drying
Paclitaxel	HP-β-CD/HCO-40	Solubility	SAS process
Metformin hydrochloride	Methocel K100M	Prolonged-release	Solvent evaporation Co-grinding
Nystatin	Lactose	Buccoadhesive	
Oleanolic acid	PVP Sodium caprate	Dissolution Permeability	SFD
Mebendazole	Low-substituted HPC	Dissolution Bioavailability	Lyophilization
Flurbiprofen	Na-CMC and Tween 80	Bioavailability	
Sibutramine	Gelatin, HPMC and citric acid	Solubility	Spray drying
Cyclosporine A	Polyoxyethylene (40) stearate	Dissolution	Solvent-melt
Nifedipine	PEO	Dissolution Cryo-milled extrudates	TSE
Indomethacin	PEG-6000, Myrj 52, Eudragit E100, lactose, mannitol, sorbitol and dextrin	Dissolution rate	

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physicochemical compatibility, the carriers should be heat stable, freely water soluble or soluble in organic solvents (ethanol, acetone, methanol, dichloromethane, etc.), non-toxic and pharmacologically inert. Dahlberg *et al.* proposed screening tool for the selection of carrier, drug concentration and process by establishing a link between surface chemical composition, powder structure and wetting behavior of SDs; by using X-ray photoelectron spectroscopy, scanning electron microscopy (SEM) and contact angles, respectively [14].

Many water-soluble and -insoluble carriers have been employed for the preparation of SDs. Few examples of water-soluble carriers are: polyethylene glycol (PEG) [15,16], PVP [10], mannitol [17], hydroxypropyl methylcellulose [18,19], poloxamer [20], lactose [17], Gelucire 50/13 [21], Kollicoat IR [22], D-glucosamine HCl [23], inulin [7], xylitol, Plasdone® S-630 and lecithin. The water-insoluble and pH-independent carriers include porous silica [13], sodium starch glycolate [24], Eudragit RSPO, Eudragit RLPO, sodium carboxymethyl cellulose [24], pregelatinized starch [24], hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate (HPMC-AS) [25] and Eudragit 4155F.

Physicochemical properties of carriers have significant impact on the stability and properties of SDs. Feng *et al.* evaluated SDs of bifendate in different polymers, including Plasdone S-630, Eudragit EPO and Kollidon® VA 64. The bifendate-Kollidon VA 64 dispersion showed highest improvement in the bioavailability of bifendate [26]. Melt extruded SD of nimodipine with Eudragit EPO showed comparable bioavailability with its brand product (Nimotop®), but the HPMC and PVP/VA dispersions exhibited much lower bioavailability [27]. Shen *et al.* investigated co-spray dried SDs of ibuprofen (IBU) with mesoporous silica of

different pore and particle sizes. The amorphous form of IBU was obtained with MCM-41 and SBA-15 (pore size smaller than 10 nm), because of nanospace confinement. By contrast, SBA-15-LP (pore size above 20 nm) provided nanocrystals of IBU [28]. Broman *et al.* prepared SDs of probucol with water-soluble polymers such as PVP, polyacrylic acid (PAA) and polyethylene oxide (PEO). The probucol was in amorphous form in PVP dispersion, while the other two dispersions PAA and PEO contained the crystalline polymorph II [29]. Felodipine dispersed as amorphous nanoparticles in PVP, whereas in PEG the dispersion was as crystalline microparticles. Increase in felodipine/carrier ratio resulted in increased drug particle size [30]. The advanced carriers such as Soluplus®, Neusilin®, Solumer™ are also introduced to prepare SDs of enhanced characteristics like stability, solubility and bioavailability.

High amount of carrier (50 – 80% w/w) is required to prepare SDs. This high amount of carrier increases the bulk of dosage form, especially when dose size is high (> 500 mg). Okonogi *et al.* prepared the high drug-loaded ternary SD by incorporating one additional component (surfactant) to the binary system. This ternary dispersion showed better dissolution as compared with binary dispersion [31].

3. Methods for preparing solid dispersions

Depending on the challenges/requirements SDs can be prepared by several methods. If one method fails to provide stable SD then other one can be utilized [32]. The methods used for preparing SDs are: kneading [33], spray drying [33], solvent wetting [33], solvent evaporation [33], agitation granulation [34], 4-fluid nozzle spray drying [19,35], twin screw extruder (TSE) [36], pulse combustion dryer system, HYPULCON [37], microwave irradiation [38,39], supercritical antisolvent (SAS) process [40], spray freeze drying (SFD) [41], lyophilization process [42], solvent-fusion method [43], KinetiSol Dispersing (KSD) [32,44], spherical crystallization technique [45], dropping method [46], near-supercritical carbon dioxide [47], ultra-rapid freezing (URF) [48], liquid-filled dispersion [49], fusion and high-shear mixing (**Table 2**).

The methods and process for preparing SDs can have great impact on dispersion characteristics. Along with process parameters (solvent system, friction force, attrition, shear, temperature, rate of cooling), the carrier composition also influences the characteristics of SD [50]. Huang *et al.* evaluated the effect of formulation and process technology on drug molecular dispersibility in SD of nifedipine with ethylcellulose and Eudragit RL. The dispersions were prepared by co-precipitation, co-evaporation and fusion methods. The order of extent of nifedipine dispersion was fusion > co-evaporation > co-precipitation [51]. Sonali *et al.* reported that co-precipitation was the best method to provide a stable amorphous SD of silymarin, followed by spray drying > kneading [52]. In a comparative study, Wu *et al.* found that SD prepared by compressed antisolvent techniques was superior in performance than dispersion obtained by spray drying technique [53]. The SD of delta-9-tetrahydrocannabinol with inulin prepared by lyophilization improves the chemical stability of delta-9-tetrahydrocannabinol [54]. The cooling rate of SDs prepared by the melt method also influences its property (viz. crystalline form, amorphous form, molecular dispersion, dissolution rate, etc.) [55,56].

3.1 Kneading

The physical mixture of drug and carrier is triturated to thick paste using small volume of solvent. The solvent used can be organic (alcohol, dichloromethane, acetone) or aqueous (water) or mixture thereof. The kneaded paste is dried in oven or vacuum oven and the dried mass is pulverized and stored in desiccator [57]. Kneading process is economical but residual solvent may be an issue.

3.2 Spray drying

In conventional spray drying process, the drug and carrier are dissolved or dispersed in a common solvent and atomized in a drying chamber with hot drying gases. The properties of SD prepared by spray drying method are influenced by solvent composition (organic or aqueous or mixture thereof), atomization efficiency, consistency of feed material, rate of drying, drying gas flow rate, inlet temperature, size of atomized droplets. The physicochemical properties of drug and carrier also influence the characteristics of SD [58].

3.3 Solvent wetting

The poorly water-soluble drug is dissolved in organic solvent (ethanol, isopropyl alcohol), and this solution is added dropwise to the carrier material and mixed properly. After proper mixing, the solvent is evaporated and the dried mass is grounded and pulverized [59].

3.4 Solvent evaporation

The drug and carriers are dissolved or dispersed in common solvent (or solvent mixture) and then solvent is evaporated with the help of heat, with or without vacuum. The dried solid mass is crushed, pulverized and stored in desiccator. There are several factors which may affect the dispersion characteristic, some are listed as: drug-to-carrier ratio, carrier type, solvent composition, rate of evaporation, temperature of evaporation [60].

3.5 KinetiSol Dispersing

KSD is a new fusion-based process where no external heat is applied. The mixture of drug and carrier is subjected to high shear and frictional forces where it gets melted. In KSD, a circular processing chamber is fitted with a rotating shaft having blades protruded toward the chamber wall. The composition is loaded into chamber at room temperature, and allows the blades to rotate at high speed. These rotating blades generate heat through friction and shear, and temperature within chamber is increased. After achieving the predetermined

Table 2. Summary of methods used to prepare SDs.

Method	Description	Carrier	Advantage	Disadvantage
Melting or fusion	Heat melted mixture of drug and carrier is cooled and pulverized	PEGs, mannitol, urea, poloxamer	Simple and economical	Incomplete miscibility Thermolabile
Hot-melt extrusion	Drug–carrier mixture is melted, homogenized and extruded	CP, HPMCP	Continuous process	Immiscibility Thermolabile
Solvent evaporation	Drug and carrier dissolved in solvent, solvent evaporated under vacuum	PVP, Pluronic F68, mannitol, lactose, urea	Low temperature prevents thermal decomposition	High cost. Ecological issues
Melting solvent	Drug dissolvent in solvent added to melted carrier	PEGs	Low-dose drug dispersed uniformly	Limited to low-dose drugs
Spray drying	Drug and carrier dissolved in solvent are spray dried	HPMC, HPMC-AS/PHPMA, PVP	Uniform spherical particles	Expensive Slow process
Comminution	Drug and carrier comminuted	HPC (SSL)	Simple and economic	Physical stress
Kneading	Moisten mass of drug and carrier is kneaded	Poloxamer 188	Simple and economic	Uniformity
Electrostatic spinning	Electrical forces across liquid stream of drug/polymer solution overcome surface tension and fibers are formed	HPMC	Preparation of nanofibers	Scale-up
Liquid-filled dispersion	Liquid melt of SD filled in hard gelatin capsule	Polysorbate-80, phosphatidyl choline	Avoid grinding- and drying-induced changes	Thermolabile Changes in crystallinity
Fluidized bed coating	Drug–carrier solution spray coated on to sugar spheres	HPMC	Scale-up	Lengthy process
Lyophilization	Drug–carrier are co-dissolved in solvent, frozen and sublime the solvent	L-HPC, skimmed milk	Low temperature	Economical issue
Melt agglomeration	Heat the binder–drug–excipient mixture above the melting point of binder, and agglomerate	PEGs, Poloxamer 188, Gelucire 50/13	Homogenous distribution	Not suitable for low melting carriers or high melting binders
SCF	Organic solution of drug–carrier sprayed into a continuous supercritical phase or Drug and carrier dissolved in CO_2 is sprayed into expansion chamber	HPMC, PVP	Low temperature Solvent free	Scale-up
Co-precipitation	Drug and carrier are co-precipitated from its solution by adding non-solvent	Acrylic polymers, PVP	Simple	Economical issue
Dropping	Melted drug–carrier mixture is pipetted and then dropped and solidifies on plate	Gelucire 44/14, TPGS-1000	Simple	Scale-up Thermolabile
Pulse combustion dryer system HYPULCON	Liquid dispersion of drug & carrier is atomized and dried in combustion chamber	Kollidon®	Instantaneous drying Low temperature drying. Low cost	
Microwave irradiation	Heating drug–carrier mixture through microwave radiation	Vitamin E TPGS, Gelucire 50/13 Poloxamer 188	Solvent free Short heat exposure	Scale-up
SFD	Drug and carrier solution was sprayed onto liquid nitrogen	Inulin, PVP, Pluronic F68	Low temperature	Scale-up

CP: Carbopol; HPMC-AS: Hydroxypropyl methylcellulose acetate succinate; KSD: kinetiSol Dispersing; PEG: Polyethylene glycol; PHPMA: Poly[*N*-(2-hydroxypropyl)methacrylate]; PVP: Polyvinylpyrrolidone; SCF: Supercritical fluid; SD: Solid dispersion; SFD: Spray freeze drying; URF: Ultra-rapid freezing.

Table 2. Summary of methods used to prepare SDs (continued).

Method	Description	Carrier	Advantage	Disadvantage
KSD	Drug and carrier mixture is melted in KSD and molten material is ejected into liquid nitrogen	Eudragit L100-55, AQOAT® LF, Carbomer 974P	Provides plasticizer free, stable, amorphous dispersions	
URF	Liquid dispersion of drug and carrier is frozen on cryogenic substrate (-45°C), the frozen droplets are lyophilized	Mannitol, SDS, enteric polymers	Low temperature	Scale-up

CP: Carbopol; HPMC-AS: Hydroxypropyl methylcellulose acetate succinate; KSD: kinetiSol Dispersing; PEG: Polyethylene glycol; PHPMA: Poly[*N*-(2-hydroxypropyl)methacrylate]; PVP: Polyvinylpyrrolidone; SCF: Supercritical fluid; SD: Solid dispersion; SFD: Spray freeze drying; URF: Ultra-rapid freezing.

temperature, the molten mass is directly ejected into liquid nitrogen for rapid quenching. The quenched material is held under vacuum for about 30 min to prevent moisture absorption [32].

3.6 Fusion

Drug and carrier mixture is melted under stirring at a temperature near to their melting point. The uniformly mixed melted mass is allowed to cool at room temperature or under cool conditions. The cooling rate may have great impact on the characteristics and stability of SD. The solidified mass is pulverized and stored in desiccator [61].

3.7 Agitation granulation

The drug and binder solution (granulation fluid) is added to the carrier or mixture of carriers and then the mixture is granulated in high-speed agitation granulator. The resulting granules are dried in a fluid-bed dryer and dried granules are passed through sieve [34].

3.8 4-Fluid nozzle spray drying

4-Fluid nozzle spray drying generates more uniform particle size as compared with conventional spray drying. According to this technique, two different solutions can be sprayed at same time. The machine is equipped with two routes for gas supply and two routes for liquid-feed. The gas and liquid are instantaneously mixed; liquid extended by the gas is atomized in the shock waves that arise from the collision focus of the edge tip [19,35]. The outline diagram of 4-fluid nozzle spraying is shown in **Figure 1**.

3.9 Twin screw extruder

TSE is one of the commonly used methods for preparing SD. The TSE comprises hopper, kneading screw, barrel, a die and heaters. Heaters are used to control temperature inside the barrel. Uniformly mixed composition (drug and carriers) is introduced into the hopper of TSE. This mixture from hopper is carried forward by feed screw into the barrel and kneaded under high pressure with the help of kneading screw. The water can also be supplied into the mixture by using injection port. The kneaded mixture is extruded through dies. The extrudes are dried, pulverized and stored [36]. Kneading elements of screws play very important role in changing the characteristics of SD. The operating conditions also influence the physicochemical properties of the extruded material (SD). Slow revolution of screws and the addition of a suitable amount of water to the mixture increase the rate of drug dissolution [36,62]. The outline diagram of TSE is shown in **Figure 2**.

3.10 Microwave irradiation

Microwave energy has been employed to heat or melt the materials. The polar molecules (electric dipoles) rotate and try to align themselves with the alternating electric field of the microwaves. These rotating polar molecules hit other

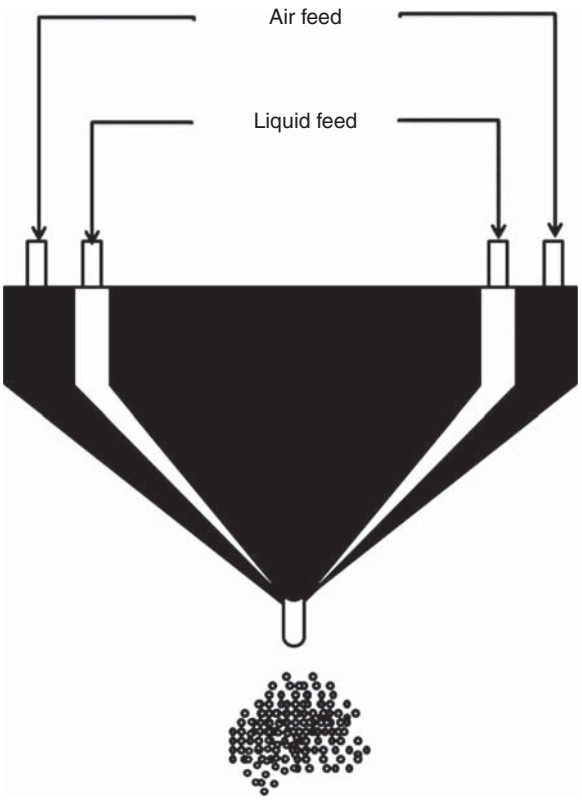

Figure 1. Outline diagram of 4-fluid nozzle spray drying.

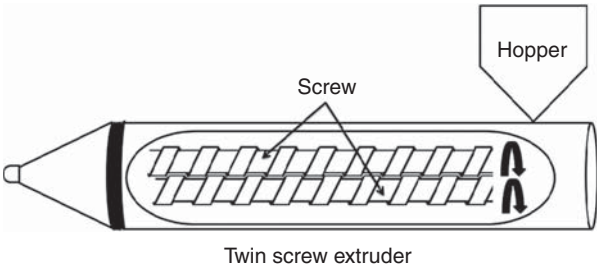

Figure 2. Outline diagram of twin screw extruder.

molecules and put them into motion, resulting in dispersion of energy in the form of heat. This property of microwaves has been exploited to heat and dry various materials. The new application of the microwave irradiation in the field of pharmaceutics is preparation of solvent-free SDs and converting crystalline state of a drug into amorphous state. The uniform physical mixture of drug carrier is subject to microwave irradiation until it gets converted into homogenous mass. After microwave exposure, the mass is cooled and pulverized. The characteristics of end material (SD) are influenced by several factors, such as: drug:carrier ratio, microwave power and duration of irradiation. Microwaves irradiation offers several advantages, such as: rapid and uniform heating, environmental control, energy saving and low operating cost. In addition to this, another advantage of microwave irradiation is to prepare the binary, ternary or quaternary systems without using any organic or aqueous solvents. The end product of microwave irradiation is almost free from residual solvents. Moneghini *et al.* prepared microwave-assisted SDs of nimesulide, and IBU, in which the solubility and dissolution of drug was enhanced [63,64].

3.11 Dropping method

The dropping method has been used previously to facilitate the crystallization of different chemicals. The method has also been employed for the production of round particles of SD from melted material. Melted drug–carrier mixture is pipette and then dropped onto a plate where it solidifies into round particles or hemispherical pellets. The product properties are influenced by drop size, rate of cooling, porous–non-porous surface, drug–carrier ratio and viscosity of melt. The viscosity is temperature dependent so it is very important to adjust the temperature in order to achieve the instant solidification of the droplet and to get the spherical-shaped particles. The use of carriers that solidifies at room temperature may aid the dropping process. Generally, the stainless steel plates are used for the dropping purpose because of its optimal surface energy, which results in the formation of round particles. This is a cost-effective method, which simplifies the production process by avoiding the hard pulverization, sifting and compressibility difficulties encountered with the other melt methods. Like microwave irradiation and other melting methods, the dropping method also does not use organic solvents and therefore has none of the problems associated with residual solvent or solvent evaporation. The dropping method is not suitable technique for preparing SDs of thermolabile materials. SDs of atorvastatin and meloxicam were prepared by using dropping method [46,65].

3.12 Spray freeze drying

SFD involves spray freezing on cryogenic liquid surface, or into cryogenic liquid, followed by freeze drying. In this method, the small frozen droplets are produced by spraying or atomizing drug–carrier solution or suspension into a cryogenic liquid, such as liquid nitrogen. The resulting frozen droplets are freeze-dried in a conventional freeze dryer. The critical parameters for the optimization of this process are feed rate of drug–carrier solution and atomization airflow. These parameters should be taken into consideration to get the optimal size droplets because the smaller size droplets will increase the surface area which results in increased dissolution. The freezing and drying conditions also influence the final product as it may control the porosity of droplets. The main advantage of SFD is that thermolabile materials can be processed by this method. Major disadvantage of SFD is that the process is lengthy and

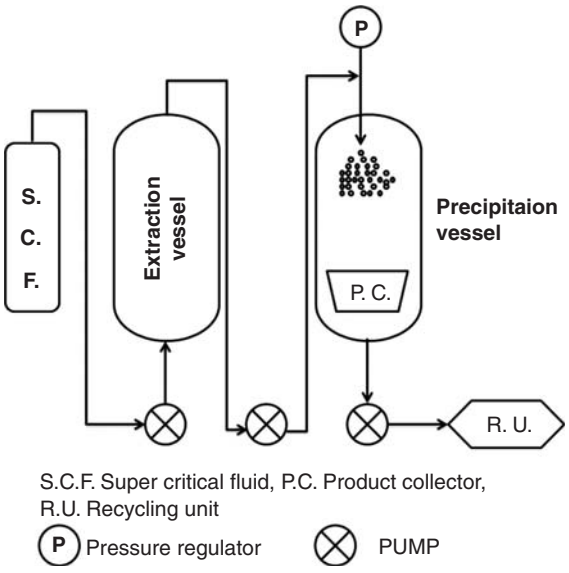

Figure 3. Outline diagram of supercritical antisolvent process.

expensive. The bioavailability of poorly soluble drugs such as carbamazepine, danazol, baicalein and oleanolic acid has been enhanced by this method [41,66-68].

3.13 Freeze drying

Freeze drying or lyophilization is a convenient but lengthy unit operation to prepare dry SDs of thermolabile or biological materials. Lyophilization involves freezing, primary drying (ice sublimation) and secondary drying. The uniform mixture of drug–carrier dissolved in a suitable solvent system is frozen under controlled conditions. This frozen material is subjected to freeze drying in suitable freeze dryers. Primary drying takes place under low vacuum, chamber pressure is retained below the vapor pressure of ice and the ice is transferred from frozen material to the condenser by sublimation. The secondary drying takes place at elevated temperature and low pressure to desorb the water from the dried material. All three stages are very critical and important and should be optimized properly. Lyophilized products are mostly amorphous and moisture sensitive, and may crystallize if exposed to moisture. Though the method is expensive and time consuming, but preferred for the preparation of SD of thermolabile materials. The SDs of glyburide and docetaxel were prepared by using freeze drying method [69,70].

3.14 Supercritical antisolvent process

SAS process is used to prepare SD of small particle size with better flowability and having least or no residual organic solvents. The SAS process involves a supercritical fluid (SCF), which is used as antisolvent to the solute and solvent to the liquid. The SCF precipitates the solute from the liquid solution and dissolve the liquid solvent. The organic solution of drug–carrier mixture is sprayed into a continuous supercritical phase or the drug–carrier mixture dissolved in SCF is sprayed into the expansion chamber. The outline diagram of SAS process is shown in **Figure 3**. SCF is a substance existing as a single fluid phase above its critical temperature and critical pressure. There are number of SCF, for example, nitrous oxide, water, methanol, ethanol, ethane, propane, *n*-hexane, CO_2 and ammonia. Carbon dioxide is the most commonly used fluid, as it is chemically inert, non-toxic, non-flammable and abundant. Owing to its mild critical temperature (31.06°C) and critical pressure (73.8 bar), CO_2 is a suitable SCF for heat-sensitive substances like peptides, steroids. SAS process is environment friendly and uses non-toxic solvent. The products prepared by this process are also safe and almost free from residual solvents. This technique has been used to prepare SDs of numerous drugs; some of them are oxeglitazar, furosemide and carbamazepine [71-73].

3.15 Ultra-rapid freezing

URF technology produces small particles with high surface area. The URF enhances the dissolution rate and bioavailability of poorly water-soluble drug substances. Briefly, the process involves freezing a drug–carrier solution onto the surface of a cryogenic substrate, collecting the frozen particles and removing the solvent. URF technology has the potential to create SDs with better physicochemical properties. Solid dispersions of repaglinide and tacrolimus were prepared by this method [74,75]. Overhoff *et al.* prepared the enteric-coated SD of itraconazole using URF technique [48].

3.16 Pulse combustion dryer system, HYPULCON

Wang *et al.* explored the application of pulse combustion dryer for preparing SDs. Powerful shock waves are generated by using pulse engine. The combustion air and gaseous fuel are ignited to explode and produce hot, high-pressure gases. These hot gases form shock waves and rush toward the atomizer. The more fuel and air enters and explodes again and again due to the hot gases left in the channel. This combustion cycle repeats itself to produce consecutive high-temperature shock waves. The drug–carrier solution is sprayed by the atomizer into high-speed combustor exhaust gases produced by the pulse engine and is dried by the actions of shock waves, ultrasonic waves, gas flow and gas temperature in the drying chamber. The dried material is recovered by using collection equipment, such as a cyclone and bag filter. The principles involved in the drying by pulse combustion dryer system are heat for evaporation, mechanical action of gas dynamic atomization, environment of extreme turbulence that promotes very high rate of heat transfer and dehydration through compression and contraction. The outline diagram of pulse combustion dryer is shown in **Figure 4**. The benefits of pulse combustion dryer are: quick drying at low temperature and high thermal efficiency. The dried particles are uniform in size and have superior surface characteristics [37,76,77].

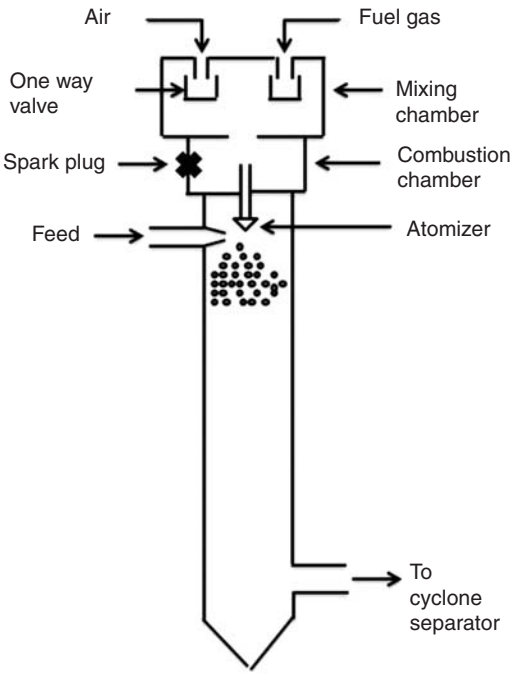

Figure 4. Outline diagram of pulse combustion dryer.

3.17 Liquid-filled dispersion

Uniformly homogeneous molten mixture of drug–carrier is filled into hard gelatin capsule by using pipette, burette or medicine droppers. The capsule filled with molten mixture is allowed to solidify and cool for some time before being capped [1]. The drugs and carriers having low melting point are good candidates for this method [49,78].

3.18 Solvent–fusion method

According to solvent-fusion or solvent-melt method, the drug solution is incorporated into molten carrier and then the mixture is suddenly cooled. The obtained cooled mass is dried and pulverized [79].

Typically, SD methods are based on three different principles: i) removal of solvent from drug–carrier solution, ii) melting or heating the mixture of drug–carrier and iii) applying mechanical stress to the drug–carrier mixture. Solvent-based processes like spray drying, solvent evaporation, pulse combustion dryer, SAS process, SFD and solvent-melt require some organic or aqueous solvent. The most commonly used organic solvents are ethanol, methanol and acetone. Different compositions and ratios of solvents like acetone–ethanol or acetone–water or ethanol–water or methanol–water may also influence the product characteristics. The main issues associated with organic solvents are toxicity, residual solvent, safety and environmental control. The choice of method or process depends on product's requirements. The spray drying is one of the most commonly used methods for preparing SD, as the process is quick, less expensive than many other processes. In spray drying process, the liquid material is atomized through the nozzle(s) under high pressure and allowed to dry in the expansion/drying chamber. Typically, spray-dried products are amorphous in nature and also have good physicochemical characteristics like particle size control, flowability, enhanced solubility and stability. The melt-fusion methods are preferred when drug and carrier are stable under heating conditions and their melting points are low. The melt-based processes are simple, cheap and almost free from residual solvents and solvents-related toxicity and hazards. But the compositions prepared by melt-based process undergo aging and are prone to moisture-related crystal growth and agglomeration. Methods based on melting are not suitable for thermolabile substances. The thermolabile substances can be processed through cryogenic methods such as lyophilization, SFD, SAS, etc. The lyophilized products also require moisture protection.

Bikiaris reviewed the progress in methodologies used for preparing SDs of poorly soluble drugs, to improve its solubility, dissolution and bioavailability. The author extensively discussed the use of inorganic porous silica nanoparticles (Sylysia) to prepare SDs, solvent evaporation, wet milling, KSD, electrospinning, supercritical methods, cyclodextrin complexation, melt mixing, kneading, spray drying, HYPULCON pulse combustion dryer. The author also elaborated the impact of process, process parameters, conditions, carriers and drug-to-carrier ratios, on the properties of SDs [80,81].

4. Characterization of solid dispersions

Solid dispersions are characterized to ensure the type of dispersion (molecular, amorphous, crystalline) uniformity, miscibility, particle size, surface properties and stability. At present, several techniques are available which are used to characterize SDs, such as: X-ray diffraction, differential scanning colorimetry, Fourier transform infrared spectroscopy, SEM, small-angle X-ray scattering and dissolution testing [21,82-85]. The confocal laser scanning microscopy can be employed to analyze the size of autofluorescent drug crystal in SD [86]. ^{1}H-NMR (proton nuclear magnetic resonance spectroscopy) spin–lattice relaxation measurements have been used to assess the miscibility of drug and excipients in SDs [87]. There are other techniques also which can be employed to analyze miscibility or heterogeneity of SDs, such as: nanothermal analysis technique [88], hot-stage microscopy [89] and atomic force microscopy [90]. Rumondor *et al.* evaluated drug–polymer miscibility in amorphous SD systems by using differential scanning calorimetry (DSC), mid-infrared spectroscopy and powder X-ray diffractometry [91]. The modulated DSC with the Gordon-Taylor model can also be used to confirm the mixing behavior of two components in a SD [92]. The techniques to characterize SD are summarized in **Table 3**. Baird and Taylor reviewed the thermal analytical techniques which

Table 3. Techniques used to characterize SDs.

Technique	Description	Application	Limitation
Powder X-ray diffraction	Measure the intensity of diffraction peaks. Sharpness of diffraction peaks indicates crystallinity	Measure degree of crystallinity and miscibility	Semi-quantitative
FTIR	Measure VB. Sharpness of VB indicates crystallinity	Measure interaction and crystallinity	Quantification in SD cannot be done
DSC and MDSC	Detect temperature of thermal events (glass to rubber transition, (re) crystallization, melting or degradation)	Measure the degree of crystallinity and miscibility. MDSC also measures molecular dispersions	Bond interaction
Confocal Raman spectroscopy	Measure the image of drug distribution	Measure homogeneity	Do not measure nano-sized drug particles
Confocal laser scanning microscopy	Fluorescent image of drug crystals are measured at a wavelength	Determine drug crystal size in powder mixture or SD	Limited to autofluorescent drugs
SEM, ESEM	Measure surface morphology of drug and carrier in dispersion	Qualitative (amorphicity and crystallinity)	Quantification cannot be done
Hot stage microscopy	Change in morphology of sample as a function of temperature	Measure miscibility	Not quantitative
Water vapor sorption	Discriminate amorphous and crystalline material on the basis of hygroscopicity change	Degree of crystallinity	Bond interaction
Dissolution/solubility testing	Comparison of dissolution/solubility of drug and SD	Predict the success of drug delivery system	Bond interaction
AFM	Fractured films are prepared by annealing and quench cooling and characterized with Raman microscopy in combination with AFM	Drug excipients miscibility and stability	Not quantitative
^{1}H-NMR	Typical spin–lattice relaxation time decay is measured in different frame	Assess the miscibility	Not quantitative
Nanothermal analysis	Map thermal properties during imaging	Measure heterogeneity	Bond interaction

AFM: Atomic force microscopy; DSC: Differential scanning calorimetry; ESEM: Environmental scanning electron microscope; FTIR: Fourier transform infrared spectroscopy; ^{1}H-NMR: Proton nuclear magnetic resonance spectroscopy; MDC: Modulated differential scanning calorimetry; SD: Solid dispersion; SEM: Scanning electron microscopy; VB: Vibrational band.

can be employed to evaluate the properties of amorphous SDs. The emphasis was put on the glass transition temperature (T_g), thermodynamic and kinetics of T_g, of factors affecting T_g, correlation of T_g and SDs stability, molecular mobility and its role in crystallization of amorphous phase, factors affecting the molecular mobility, miscibility, factors affecting miscibility, role of moisture in the re-crystallization of amorphous SDs and detecting SDs crystallinity [93].

5. Stability issues

Like other techniques, SDs also have some limitations. Some of the SDs have been reported to be unstable and non-uniform. There are many challenges in preparation of SDs, such as de-mixing, re-crystallization and formation of different forms. It has been reported that amorphous SDs are unstable on storage and undergo reverse phenomena of phase re-crystallization [94]. In some cases, particle growth takes place during dissolution of SDs; this phenomenon of reverse crystallization hampers the dissolution after burst release [95]. **Figure 5A** represents the stable, uniform SD and **Figure 5B** represents the phase re-crystallization and agglomeration in unstable dispersion after aging. **Figure 5C** shows phase separation phenomena in SD of two immiscible materials, such as the materials of opposite nature like highly lipophilic drug and highly hydrophilic carrier.

The vast range of methodologies for preparing SDs provides alternative processes which are best fit for a particular drug and carrier. Measures have been taken to prepare stable and uniform SDs. Phase separation can be minimized by rapid cooling and re-crystallization can be controlled by preparing binary or ternary dispersions. Rumondor *et al.* studied the amorphous-amorphous phase separation phenomena of amorphous SDs and observed that stronger drug–polymer interactions, low hygroscopicity of amorphous SD and less hydrophobic drug provided a stable system [96]. Ghosh *et al.* reported phase separation in SD of NVS981 and HPMCP, but the dispersion in HPMC 3cps and HPMC-AS was stable [25]. Six *et al.* prepared binary and ternary SDs of itraconazole with Eudragit E100 and PVPVA64 by using co-rotating twin-screw hot-stage extruder. The ternary dispersion was found to be of good dissolution properties and improved physical stability compared with the binary SDs [97]. On the other hand, milled melt extrudate binary

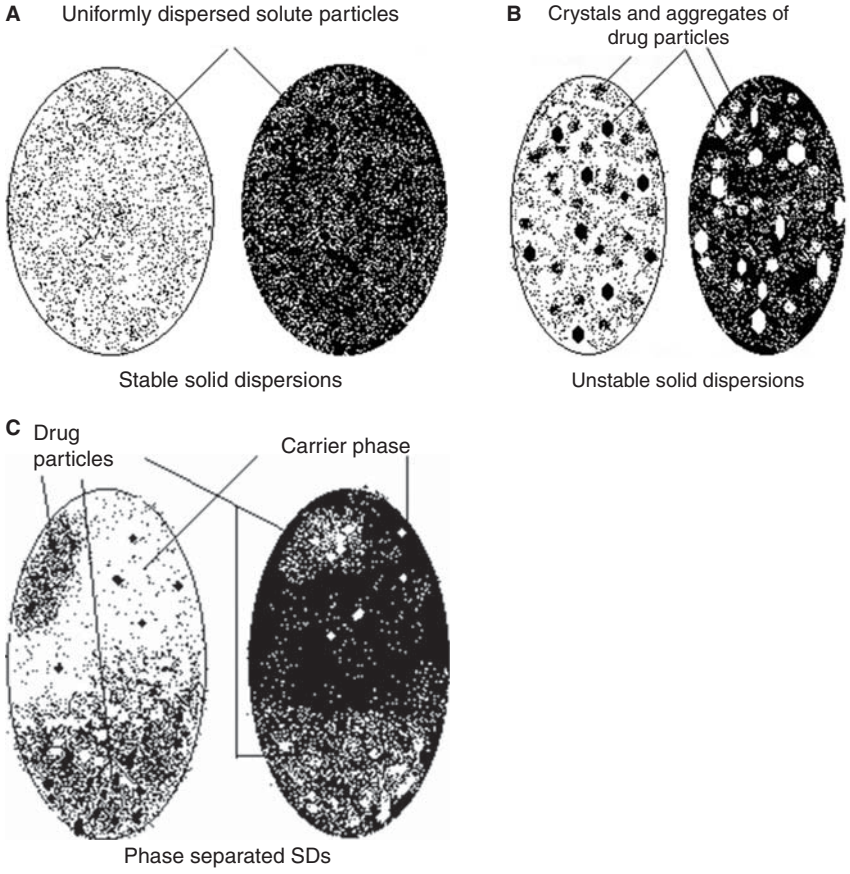

Figure 5. Representation of stable and unstable solid dispersions where 'A' represents stable solid dispersion, 'B' represents phase re-crystallization and agglomeration and 'C' represents phase separation phenomena.

SD of itraconazole and HPMC was found to be chemically as well as physically stable [98]. The ternary SDs prevent re-crystallization of amorphous form [99]. Pajula *et al.* reported that Flory–Huggins interaction parameter is a reasonably good indicator for predicting the phase stability of small molecule binary mixtures. The method can enable fast screening of the potential stabilizers needed to produce a stable amorphous binary mixture [100]. Janssens and Van den Mooter reviewed the physicochemical properties-related aspects of SDs, and elaborated the glass transition temperature (T_g), nucleation, crystal growth, stability of glass solutions, molecular mobility, phase separation, and also correlated these with the stability of SDs [101].

6. Controlled-release solid dispersions

SDs also have been employed for sustained-, delayed- or controlled-release dosage forms. The water-insoluble, sweallable or pH-dependent polymers are used as carriers. Apart from drug characteristics, carrier's solubility, cross-linking, molecular weight and its ratio with drug plays very important role in controlling the release. Controlled-release interpolymer complex SD of phenacetin with methylcellulose and carboxyvinyl polymer was examined for effect of polymer ratio and molecular weight on release profile of drug [102]. Ozeki *et al.* also prepared controlled-release SDs of phenacetin with PEO–carbopol (CP) interpolymer complex [103].

The tablets prepared from SD granules of losartan potassium and PEO provides pH-independent controlled release for over 12 h (2 h in gastric fluid and 10 h in intestinal fluid) [104]. The matrix tablets of SD of budesonide and dextran (mol. wt. 10,000) were evaluated for colon targeting [105].

The role of pH modifiers have been established in altering drug release from SD. Choice of pH modifiers depends on the acidic or basic nature of drug. The pH modifier changes the microenvironment of drug in SD, and the drug having pH-dependent solubility or dissolution shows impact on its release profile [106,107].

The SD granules of nilvadipine were incorporated in disintegration-controlled matrix tablet. The tablet maintained sustained release regardless of the change in physiological condition through the gastrointestinal tract [108].

The controlled-release dispersions are prepared by conventional methods of preparing SD, such as freeze drying, injection molding, co-evaporation and co-precipitation, spray drying, etc. The controlled-release SD of diclofenac

with ethylcellulose and chitosan were prepared by freeze drying [109]. Quinten *et al.* developed sustained-release matrix tablets of metoprolol tartrate with ethylcellulose and PEO by using injection molding technique and investigated the effect of process parameter and material composition on release profile [110]. Solid dispersion of 10-hydroxycamptothecin and PEG-6000 was incorporated in monolithic osmotic tablet. The optimized formulation provided constant release rate of 10-hydroxycamptothecin 1.21 mg/h for 12 h [111]. Dahiya *et al.* prepared extended-release SD of promethazine hydrochloride with Eudragit RLPO and Eudragit RS100 using co-evaporation and co-precipitation techniques [112]. Sustained-release SD microspheres of nitrendipine were prepared using quasi-emulsion solvent diffusion method. The sustained-release microspheres improved the bioavailability of nitrendipine [113]. Chen *et al.* prepared sustained-release SD of misoprostol with Eudragit RS and RL. The dispersion improved the stability of misoprostol [114]. SDs can be incorporated in implants for prolonged release of medicament [115]. The sustained-release SD can be combined with rapid-release SD in the same formulation, to provide desired prolonged release with fast bolus dose of immediate release [116]. Controlled-release SD of fluvastatin with chitosan provided physical and chemical stability to fluvastatin [2].

7. Solid dispersion technology

In recent past, various technologies have emerged, which provide stable and more successful SDs.

7.1 Closed-cycle spray drying

Closed-cycle spray drying (CSD) technology of Fuji Chemical Industry (Toyama, Japan) provides high drug-loaded stable SDs. The process of CSD technology: drug and inert polymer (s) are dissolved in organic solvent and spray dried to produce SD, followed by secondary drying to remove residual solvents. This technology also claims to minimize particle size and bulk density changes during scale-up. Apart from these benefits, CSD technology also provides stable SDs (stable amorphous form), increases solubility and solves post spray drying process issues [117]. The CSD technology has wide range of facilities and is flexible in operation, approximate 1 g of drug can be evaluated. Large-scale SD manufacturing can also be done at the United States Food and Drug Administration (US FDA)-approved plant having CSD technology.

7.2 Right Size™

Particle technology of XSpray Microparticles AB (Solna, Sweden) has provided SDs with improved solubility, dissolution rate, bioavailability along with reduced formulation development time. The RightSize™ particle technology uses SCF method for controlled precipitation of active ingredients. RightSize particle technology is fully scalable and can be exploited in drug manufacture. This technology can also be employed for the development of inhalation drugs, as it has good control over particle size distribution in the nanometer to micrometer size range [118,119].

7.3 Lidose® (S.M.B.)

In Lidose® (S.M.B.) technology, the drug is simply mixed with melted carrier and filled into hard gelatin capsules and then cooled under specific and constant conditions. The Lidose claims greater tolerability for non-steroidal anti-inflammatory drugs (NSAIDs), less risk gastric irritation, rapid dissolution, protection against oxidation, superbioavailable properties, less food dependence and lower variability of inter-subject absorption [120]. Lidose technology has been used in fenofibrate capsules.

7.4 Suba™

Suba™ is a SD-based novel technology used for enhancing the bioavailability of poorly aqueous soluble drug substances (viz. itraconazole). The technology utilizes various polymers having acidic functional groups [121].

The new class of excipients like Polyox WSR N-10 (Dow), Neusilin (Fuji Chemical Industry), Soluplus (BASF SE: Ludwigshafen, Germany), Solumer (SoluBest, Ness Ziona, Israel), etc. provide thermodynamically stable SD with better physical properties.

7.5 Soluplus

Soluplus, an amphiphilic polymeric solubilizer, has been developed specially for solid solutions, where it enhances the water solubility and bioavailability of poorly water-soluble drugs. Because of its high flowability and excellent extrudability, Soluplus has been used successfully for making SD by using extrusion process [122-124]. Soluplus is a non-ionic graft co-polymer, wherein PEG-6000 (13%) forms hydrophilic backbone and polyvinylcaprolactam (57%) and polyvinylacetate (30%) forms lipophilic side chain [122,124]. Soluplus forms micelles at CMC (critical micelle concentration) of > 7.6 mg/l. Soluplus provides thermodynamically stable SD with better physical properties.

7.6 Neusilin

Neusilin (Fuji Chemical Industry), an inorganic magnesium aluminometasilicate-based adsorbent, stabilizes amorphous SD of poorly water-soluble drugs, and also improves the solubility and dissolution rate [125]. The amorphous dispersion of drugs with Neusilin can be prepared by simple milling (ball mill) process [125,126]. The amorphous microporous granules of Neusilin have high adsorption capacity. Neusilin US2 is slightly neutral in nature while Neusilin FL2 and FH2 are basic (pH 8 – 10) in nature. Because of neutral nature of Neusilin US2, its compatibility range is broad. Neusilin FL2 and FH2 are preferred for slightly acidic drugs [127,128]. Silanol ring on the surface of Neusilin interacts with drug molecule and stabilizes it through hydrogen bonding [128]. Amorphous indomethacin stabilized by co-grinding with Neusilin US2, hydrogen bonding and surface interaction

Table 4. Commercially available SD formulation.

Brand name	Drug	Company name
Gris-PEG	Griseofulvin	Pedinol Pharm, Inc.
Kaletra	Lopinavir, ritonavir	Abbott
Cesamet	Nabilone	Valeant Pharmaceuticals
Intelence	Etravirin	Tibotec
Certican	Everolimus	Novartis
Isoptin SR-E	Verapamil	Abbott
Nivadil	Nivaldipine	Fujisawa Pharmaceutical Co.
Prograf	Tacrolimus	Fujisawa Pharmaceutical Co.
Rezulin	Troglitazone	Sankyo
Sporanox	Itraconazole	Janssen Pharmaceutical
Rapamune	Sirolimus	Wyeth
Tricor	Fenofibrate	Abbott
Megace ES	Megestrol acetate	Par Pharmaceuticals
Emend	Aprepitant	Merck

between metal ions of Neusilin US2 and indomethacin may be responsible for this stabilization [129]. Ketoprofen, indomethacin, naproxen and progesterone were milled with Neusilin. The crystalline acid form of carboxylic acid-containing drugs (ketoprofen, indomethacin and naproxen) converted to amorphous salt form on milling with Neusilin, whereas progesterone seems to interact via hydrogen bonding. The amorphous Neusilin-bound states of all four drugs were physically stable during storage [130].

7.7 Solumer (Solu Best)

Solumer (SoluBest) is a dual polymer-based SD technology that improves the dissolution and bioavailability of poorly soluble drugs. The lipophilic drug is solubilized in an organic solvent (viz. alcohol) and an amphiphilic and a hydrophilic polymer are separately mixed in aqueous solvent (water). These organic and aqueous solutions of drug and polymers are mixed and spray dried (Solumerization). The examples of suitable amphiphilic polymers are PEO (also referred to as PEG), PEO derivatives, PEO co-polymers such as PEO/polypropylene glycol (PPG) co-polymers, PEG-modified starches, poloxamers, poloxamines, PVP, hydroxypropyl cellulose (HPC), hypromellose (HPMC) and esters thereof, vinyl acetate/vinylpyrrolidone random co-polymers, PAA and polyacrylates. Hydrophilic polymers include sodium carboxymethylcellulose (Na-CMC), hydroxyethylcellulose (HEC), polyvinyl alcohol (PVA), sodium alginate, starch, chitosan and carrageenan. The dispersion produced by Solumer technology is free flowing, solubilized drug homogeneously into a polymer matrix, modified thermal behavior of SD, formation of nanocolloids dispersion; stable crystalline constructs enhance solubility, dissolution and bioavailability; the technology is also used for prolonged and targeted release [131,132].

Some of the commercially available SD products are enlisted in **Table 4** [80,101].

8. Summary of patents

A large number of patents have been granted for SDs. The major contributors to SD technology seem to be Japanese inventors. Okuda *et al.*, US 4,654,206 (Fujisawa Pharmaceutical Co., Ltd., Japan), prepared amorphous SD of dihydropyridine A compound in hydroxylpropylmethyl cellulose by using solvent evaporation technique. The dispersion provides fast release of dihydropyridine A compound [133]. Ueda *et al.*, US 4,916,138 (Fujisawa Pharmaceutical Co., Ltd.), prepared SD of FR-900506 in HPMC-2910, by solvent evaporation. The SD improves dissolution of FR-900506 [134]. Gupta, US 4,244,949 (The Population Council, Inc., New York, NY, USA), prepared prolonged-release contraceptive implants by using contraceptive and a lipoidal carrier (cholesterol). The implants were prepared by fusion method [135]. Kelm *et al.*, US 5,281,420 (The Procter & Gamble Co., Cincinnati, OH, USA), prepared solidified melt mixture of tebufelone with poloxamer [136]. Nakano *et al.*, US 5,340,591 (Fujisawa Pharmaceutical Co., Ltd.), prepared SDs of nilvadapine with water-soluble polymer by prolong mixing of the drug and polymer at a temperature below their melting point [137]. Nakamichi *et al.*, US 5,456,923 (Nippon Shinyaku Co., Ltd., Japan), provided a TSE process for the preparation of SDs. The invention disclosed many prolonged-release as well as delayed-release formulations [138]. Ser *et al.*, US 5,580,546/5437859 (L'Oreal, France), invented a process for preparing a cosmetic SD (lipstick), wherein the polyhydric alcohol ('polyol') was dispersed in a fatty body. The dispersion was prepared by fusion method. The uniformly mixed fused composition was molded into sticks [139,140]. Kobayashi *et al.*, US 5,556,642 (Tanabe Seiyaku Co., Ltd., Japan), prepared SD-based sustained-release microspheres of water-soluble drugs with biodegradable carriers by using solvent evaporation processes. The microspheres were loaded into o/w emulsion system [141]. Miguel-Colombel, US 5,750,120 (L'Oreal), prepared SD comprising fatty phase (wax with a melting point higher than 60°C) and polyhydric alcohol (selected from ethylene glycol, glycerol, 1,2-propanediol, diglycerol, erythritol, arabitol, adonitol, sorbitol, dulcitol, PEG 300 or polyglycerol 500) was used in a cosmetic anhydrous care base for lips [142]. Duclos *et al.*, US 5,776,495 (Laboratoires Effik, France), prepared SD by using co-precipitation method, in hydrophilic carrier like PVP [143]. Miguel-Colombel, US 5,830,444 (L'Oreal), prepared anhydrous SD of organofluorinated hydrocarbon compounds. The dispersions were used in the cosmetic formulations like lipsticks and foundations [144]. Chen *et al.*, US 5,889,051 (Development Center for Biotechnology, Taiwan), stabilized misoprostol in sustained-release SD of ammonio methacrylate co-polymers such as Eudragit RS series, Eudragit RL series, Eudragit S, Eudragit L and the mixture thereof [145]. Krape *et al.*, US 5,955,475 (Endo Pharmaceuticals, Inc., Chadds Ford, PA, USA), prepared SD of paroxetin by solvent and fusion process [146]. Terracol is the name of inventor. The

is no inforavailable about company. The address for Terracol D. is Verrieres-le-Buisson, FR. Terracol *et al.*, US 6,027,747, provided a solvent evaporation process for the preparation of SD. The process involved the slow evaporation of organic solvent at increased pressure and then the pressure was suddenly decreased which led to quick evaporation and formation of foam [147]. Morita *et al.*, US 6,156,343 (Akzo Nobel NV, the Netherlands), used SD of nifedipine with HPMC in controlled-release tablets [148]. Miyamoto *et al.*, US 6,171,599 (Nissan Chemical Industries, Ltd. and Zeria Pharmaceutical Co., Ltd., Japan), provided a process for preparing amorphous SD of efonidipine HCl with HPMC-AS. The process included step A: of a heat treatment (85 – 140°C) or a mechanical step (0 – 140°C) and a step B: of dipping treatment into water-containing solution, impregnation treatment with water-containing solution or contacting treatment with water vapor-containing gas, or treating the mixture hot steam (100 – 140°C) and a high pressure [149]. Guitard *et al.*, US 6,197,781/6,599,535 (Novartis AG, Switzerland), prepared rapamycin/ascomycin SD by using spray drying technique [150,151]. Dittgen *et al.*, US 6,238,284 (Jenapharm GmbH & Co. KG and LTS Lohmann Therapie-Systeme AG, Germany), incorporated SD of drug in transdermal systems [152]. Makoto *et al.*, US 6,254,889 (Kyowa Hakko Kogyo Co., Ltd., Japan), prepared SD of xanthine derivatives with enteric polymers (methacrylic co-polymer L, HPMCP, HPMC-AS, carboxymethylethyl cellulose) by using fluidized bed coating and biaxial extruder (hot-melt kneading) processes [153]. Walele *et al.*, US 6,261,713 (Finetex, Inc., Elmwood, NJ, USA), prepared sunscreen SD of micronized zinc oxide and titanium oxide with carrier selected from stearyl benzoate, behenyl benzoate, arachidyl benzoate by using melting process [154]. Sherman, US 6,444,225 (Sherman; Bernard Charles, Canada), prepared bioavailability improved SD of fenofibrate with super-disintegrant by melting process. The super-disintegrant was added to the melted fenofibrate and the melted mixture was resolidified [155]. Inamori *et al.*, US 6,444,649 (Mitsubishi Chemical Corp., Japan), improved the water solubility of sialic acid derivatives by making solid with water-soluble carrier. The SDs were prepared by spray drying and solvent evaporation method [156]. Miyamoto et al., US 6,462,093 (Nissan Chemical Industries, Ltd.), provided a method for the preparation of SDs of sparingly water-soluble drugs. The drug subjected to heat treatment or mechanochemical treatment with amorphous state-inducing agent and amorphous state-stabilizing agent. The heat treatment was given by using microwaves of different frequencies [157]. Ronsen *et al.*, US 6,503,927 (Pentech Pharmaceuticals, Inc., Rolling Meadows, IL, USA), prepared stable SD of paroxetine HCl by using vacuum evaporation, rotary evaporation and spray drying techniques. The stable composition comprised paroxetine HCl, PVP and citric acid [158]. Breitenbach *et al.*, US 6,599,931 (Abbott GmbH & Co. KG, Germany), provided a method/test system for identifying bioactive substances which were capable of forming stable solid solutions or SDs in PVP. According to this method, one or more bioactive substances were mixed with 1,3-*bis*(1-pyrrolidonyl) butane to form a solution or dispersion. The dispersion of substance with 1,3-*bis*(1-pyrrolidonyl) butane was assessed spectroscopically. The dispersions which did not re-crystallize out of the solution or dispersion were selected for PVP-based SDs [159]. Appel *et al.*, US 6,706,283/7,550,158 (Pfizer, Inc., New York, NY, USA/Bend Research, Inc., Bend, OR, USA), incorporated amorphous SD of sparingly water-soluble drug into a controlled-release osmotic system. The SD core was coated with non-dissolving and non-eroding coating that controls the influx of water to the core so as to cause extrusion of a portion of the core with the help of osmotic agent [160,161]. Jennewein *et al.*, US 6,727,243 (Biochemie Gesellschaft m. b.H., Austria), prepared a SD of cefuroxime axetil, where the gelation of cefuroxime axetil on contacting with water was inhibited [162]. Takano *et al.*, US 6,753,330 (Kowa Co., Ltd., Japan), provided SD of 2-benzyl-5-(4-chlorophenyl)-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one with hydroxy propylmethyl cellulose, and polyoxyethylene polyoxypropylene glycol, which has excellent dissolvability and dissolution stability alike. The dispersion was used in rapidly dissolvable compositions [163]. Tanno *et al.*, US 6,872,336 (Shin-Etsu Chemical Co., Ltd., Japan), developed a solvent evaporation method in which the drug solution in a plasticizer and aqueous polymer solution were sprayed separately but simultaneously, onto the fluidized carrier [164]. Hayes *et al.*, US 6,881,745 (F. H. Faulding & Co. Ltd., Australia), prepared a spray-dried SD of itraconazole with HPMCP (the polymer comprising at least one acidic functional group) [165]. Yamashita *et al.*, US 6,884,433 (Fujisawa Pharmaceutical Co., Ltd.), prepared sustained-release formulation comprising tacrolimus SD [166]. Takagi *et al.*, US 6,899,899 (Yamanouchi Pharmaceutical Co., Ltd., Japan), incorporated spray-dried SD of poorly water-soluble drug with gelling polymer (HPMC) into a rapid disintegrating tablet [167]. Cabrera, US 7,112,336 (Bayer HealthCare LLC, Tarrytown, NY, USA), prepared taste masked SD of micronized quinolinecarboxylic acid or micronized naphthyridonecarboxylic acid with shellac [168]. Fort *et al.*, US 7,364,752 (Abbott Laboratories, Albania), provided a stable SD of ritonavir in PEG, the dispersion improved the bioavailability of ritonavir [169]. Jacobs *et al.*, US 7,713,548 (Sanofi-aventis U.S. LLC, Bridgewater, NJ, USA), provided stable amorphous SDs of the active drug substance with stabilizing polymers such as hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate succinate and a polymethacrylate. The SD was prepared by using spray drying technique [170]. Holm, US 7,994,214 (Lifecycle Pharma A/S, Denmark), prepared a SD of tacrolimus in PEG (mol. wt. at least 1500) and poloxamer. The dissolution rate and bioavailability of tacrolimus was improved. The dispersion was prepared by spray loading of tacrolimus–PEG–poloxamer dispersion onto solid carriers such as lactose [171].

Lippold *et al.*, US 8,021,688 (Knoll GmbH, Germany), provided quaternary SD comprising drug, PVP (mol. wt. < 1,500,000 Da), PEG (semisolid or solid at 17 – 22°C) and PEG (mol. wt. 950 – 3300 Da) [172]. Berndl *et al.*, US 8,025,899 (Abbott Laboratories, Abbott Park, IL, USA), provided bioavailability improved SDs of ritonavir and lopinavir in a water-soluble polymer having a T_g of at least 50°C (copovidone), and sorbitan monolaurate (surfactant). The dispersion was prepared by using TSE [173].

9. Conclusion

Over the years, SD has been proved to be a potential technique to enhance solubility, dissolution and bioavailability of poorly soluble drugs. Its further application has been successfully tried for controlled-release and stability enhancement of drugs. Apart from these achievements, there are still numerous challenges such as scale-up, preparation of stable, uniform, miscible SD. Some of the challenges can be managed by selecting suitable method and process conditions, carrier type, mixture of carriers, drug-to-carrier ratio and controlled environmental conditions. Multicarrier-based SD (ternary and quaternary) approaches have been found to be quite successful, as it may provide better solubility, dissolution and stability.

10. Expert opinion

SD technology has proved to be a good alternative to mechanical particle size reduction for enhancing solubility, dissolution and bioavailability of poorly soluble drugs (especially BCS class II). The products of many poorly soluble drugs are formulated easily through this technology. SD processes are simple, easy, scalable and convenient; and many of them can be carried out in institutional laboratories. The earlier SDs were unstable and difficult to process in large scale because of poor handling and flow properties. These old dispersions were monophasic, wherein the composition included one drug dispersed in one carrier. Since the introduction of multiphasic (binary or ternary) SDs, the formulation scientists gain faith in the technology. In binary SDs, drug is dispersed in two carrier materials, and in ternary the drug is dispersed in three carrier materials. The extra carrier material of binary and ternary SDs stabilizes the dispersions by preventing agglomeration of solute particles or by inhibiting re-crystallization of solute particles, or assist in solubility enhancement. The characteristics of SDs depend on degree of interaction between drug and carrier, type of interaction, drug-to-carrier ratio, the process used, process conditions such as temperature, composition of solvent, rate of cooling, environmental conditions like humidity, gap between hydrophilic and lipophilic nature of drug and carrier. Several spray drying or modified spray drying, TSE, freeze drying or modified freeze drying and SAS methods are introduced to prepare stable SD with good physicochemical characteristics. HYPULCON pulse combustion dryer system is a new addition to the SDs methods. This drying system is claimed to be economical, quick and having good control over particle size distribution. In recent past, many pharmaceutical companies have entered into the area of SD technology. Numerous SD technologies such as CSD, RightSize, Lidose and Suba have been introduced recently claiming several benefits such as size uniformity, stable dispersions, scalability, provide particle size in nanometers. Some carrier systems like Soluplus, Neusilin, and Solumer have also been developed which are suitable to prepare thermodynamically stable amorphous SDs with improved processability, solubility and bioavailability. Apart from all these successful SD technologies, still there is a need to improve the physicochemical stability of SD and to develop some more methods and polymers which can stabilize the amorphous SDs and improve the bioavailability of poorly soluble drugs. Case-by-case carrier screening methods should also be developed which can be utilized to find out drug–carrier interaction such as precipitation or crystallization, at developmental stages. Further, there is lack of understanding about crystallization kinetics of SDs; suitable techniques should be developed to make it more clear at pre-formulation stage.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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