

# Solid Dispersion as a Technical Solution to Boost the Dissolution Rate and Bioavailability of Poorly Water-Soluble Drugs

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## ABSTRACT

Solid dispersion (SD) is one of the oldest and widely utilized techniques to improve the solubility of slowly dissolving drugs. A variety of pharmaceutically compatible additives using different emerging technology is used for preparing SDs. Multiple approaches were designed to prepare SDs by such as kneading, co-milling, fusion, solvent evaporation and various solvent-associated methods. The selection of appropriate preparation method and carrier is vital for producing a homogenous product affecting its stability and biological activity. Many attempts were recently carried out to improve the scalability of the applied approaches and the results were novel preparation methods such as KinetiSol, Electrospinning and Hot-melt extrusion. In the present review, drug carriers used to formulate SD were classified as small molecular weight carriers, large molecular weight named polymeric carriers and functionalized polymeric ones. Moreover, new attractive SD formulated using the newly emerged natural carriers recently joined the field of the pharmaceutical industry.

**Key words:** Solid dispersion, Solvent evaporation, Fusion, Co-milling, Kneading, Electrospinning, KinetiSol®.

## INTRODUCTION

Drug delivery via the oral route is the most commonly applied administration method due to its ease of administration, flexible handling, cost-effectiveness, thus increasing good patient compliance.<sup>1-3</sup> Low bioavailability of poorly water-soluble drugs is considered a frequently occurring limitation for 40% of the new chemical entities resulting from the low solubility and low dissolution rates of poorly water-soluble drugs in the aqueous gastrointestinal fluids.<sup>2</sup> The drug dissolution in the gut fluids is the rate-limiting step in determining the bioavailability of the Biopharmaceutical Classification System (BCS) class II of drugs since these drugs are permeated through the gut mucosa.<sup>4</sup> The dissolution rate and, consequently, bioavailability can be boosted by different techniques, including physical, chemical modifications and inclusion into carrier systems. The technique applied to a

drug into a hydrophilic carrier generating more soluble products is called SD.<sup>5</sup>

Considering the SD technology, many researchers have issued various Classification of SD product based on preparation methods and the carrier's nature and generation. Herein, the article tried to concentrate on the most applicable methods with high yield production. A new classification simplified diagrammatically was made to explain the recent updates.

### Applied strategies for dissolution rate enhancement

The adopted strategies to enhance drug solubility and dissolution rate are generally classified into physical and chemical modifications; besides, carriers systems and media modifications are shown in Figure 1.<sup>2,5-7</sup>

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Dissolution enhancement via SD technique is one of the most direct and frequently utilized methods to improve the drug absorption rate into the systemic circulation. The term solid dispersion refers to those solid products (either amorphous or crystalline) most frequently formed by incorporating a hydrophobic drug into a hydrophilic carrier.<sup>8</sup> The drug spreads in the chosen polymer resulting in six different types of dispersions that vary according to the molecular arrangement, which affects the properties of the prepared SD.<sup>9</sup>

### Advantages and disadvantages of solid dispersions

SDs have various benefits and drawbacks, as presented in Table 1.<sup>5,10-13</sup> Classification of SDs according to the recent advances:

#### First-generation solid dispersion

In this type, the dispersion system is formed by drug incorporation into crystalline carriers such as urea and sugars, creating a slowly releasing thermodynamically stable crystalline SD.<sup>14-16</sup> The eutectic mixture was the first SD to be formulated. The monotectic mixture is not favored since the product and carrier melting points are unaffected. In contrast, the eutectic dispersion has a lower melting point than the carrier and drug melting points. The product and carrier will instantly crystallize during the cooling phase of the eutectic mixture, so it is preferred over the monotectic mixture.<sup>15,17</sup> The reduced particle size increases the specific surface area, thus enhances the dissolution rate and bioavailability.<sup>17</sup>

#### Second generation solid dispersion

This generation contains amorphous carriers and is favored over the first generation for their thermodynamic stability, such as PolyVinyl Pyrrolidone (PVP) and Poly Ethylene Glycol (PEG).<sup>15,18</sup> Amorphous carriers can be either synthetic or natural polymer. Based on the drug's physical state, amorphous solid dispersion (ASD) can be classified as amorphous solid suspensions, solutions (glass solutions), or a mixture of both.<sup>18,19</sup> Amorphous solid suspensions consist of two separate phases due to the limited solubility of the dispersed drug in the chosen carrier.<sup>20</sup> While in the amorphous solid solutions, the ingredients are molecularly dispersed into one homogenous phase.<sup>21</sup> Upon storage, the drug may recrystallize, producing less dissolving crystals. Although using more viscous polymers can impede the drug dissolution rate, it is often used to tackle the recrystallization drawback providing a more stable formulation suitable for manufacture.<sup>17</sup>

#### Third generation solid dispersion

In this generation, the carrier is supposed to have a surface activity or emulsifying activity to tackle drug nucleation and agglomeration.<sup>5,16</sup> This feature prevents recrystallization while, enhances the dissolution rate, physical and chemical stability of the formulated drug.<sup>22</sup> Gelucire 44/14 and Solutol HS 15 are two examples of surfactants used to enhance the drug dissolution rate, while polymers of low glass transition temperature ( $T_g$ ) such as poloxamer ( $P_{188}$ ) can inhibit recrystallization.<sup>22-24</sup>

#### Fourth-generation solid dispersion

In contrast to ASDs, the fourth generation of dispersions is Controlled Release Solid Dispersions (CRSD). The proposed carriers such as Hydroxy Propyl Cellulose (HPC) and Eudragit RS are used to sustain the release of biologically short half-life drugs.<sup>14,25</sup> Solubility enhancement and extending the drug release in a controlled manner are the main targets of the CSRSD.<sup>25</sup>

#### Classification of solid dispersion according to the drug dispersion into the carrier

SDs are classified into six types according to the crystal state of carriers and incorporated drugs, including eutectic mixture,<sup>26</sup> solid solutions,<sup>27</sup> glass solutions,<sup>28</sup> glass suspensions,<sup>29</sup> and amorphous precipitates of the drug in the crystalline carrier<sup>11</sup> and complex or new compound formation.<sup>30</sup> According to the molecular size of the drug, the solid solutions system is generally classified as substitutional and interstitial solid solutions.<sup>11</sup> These

**Table 1: Advantages and drawbacks of solid dispersions.**

Pros	Cons
Dissolution rate and bioavailability are enhanced through: Increase in the exposed surface area as a result of particle size reduction The conversion of the crystalline state into a more soluble amorphous state Increasing wettability Increasing porosity	Not commonly used as a commercial product because of the conversion of the amorphous drug into the less soluble crystalline form since the exposure to moisture during storage and consequently increased drug mobility can lead to phase separation and instability
Using sugar carriers can mask the bitter taste of some drugs	2. large-scale production is limited due to expensive preparation methods
Easily applicable when incorporated into a fast-disintegrating tablet (FDT)	3. Reproducibility cannot be guaranteed 4. Incorporating SDs into some dosage forms is challenging

classes are illustrated in Figure 2 in which the number of phases physical state of each component is indicated.

### Mechanism of drug incorporation and release from solid dispersion

Theoretically, when drug and polymer are in close contact at the molecular level, the drug molecules are introduced into the gaps within the loosened polymeric chains. Loosening polymer chains is necessary to incorporate the drug molecules, as the effect of heat achieves this flexibility, whether by hot-melt extrusion or fusion method.<sup>17</sup> Many techniques are based on using solvents, such as solvent evaporation and co-precipitation methods. The used solvent has a dual role: besides converting the drug into a molecular state, the solvent creates weak inter- and intra-molecular cohesion polymer chain interactions, developing polymer interactions with different solvents.<sup>8</sup>

One effective strategy for dissolution enhancement is converting the crystalline form of a poorly soluble drug into an amorphous state.<sup>31,32</sup> Thus, the drug release mechanism is dependent on the type of the dispersion system, which are different generations of ASD and CRSD.

### Drug release from ASD

The drug release from ASDs is a process that can be classified into three groups according to the drug-carrier

release rate into carrier-controlled, drug-controlled and dissolution-controlled release.<sup>33</sup> In the carrier-controlled release, water penetrates the polymer forming a viscous gel layer, from which the drug is slowly released. While in the case of drug-controlled release, the amorphous drug dissolves at a controlled rate after the polymer is initially dissolved into the dissolution medium.

The dissolution-controlled release is characterized by the simultaneous release of drug and polymer into the dissolution medium, leading to a significant super saturation effect. Here, the polymer in solution is essential to stabilize the supersaturated state. The super saturation concentration is controlled by the drug amount and the volume of the release medium.

### Drug release from CRSD

The fourth-generation solid dispersion release profile shows a controlled dissolution behavior different from the first three generations. In this generation, the CRSD releases the drug into the medium via diffusion- and erosion-based mechanisms as illustrated in Figure 3.

### Solid dispersion preparation techniques

SDs can be prepared through different approaches including kneading, co-milling, fusion, solvent evaporation and solvent melting techniques. These methods are classified according to their scalability into lab and large-scale techniques, as shown

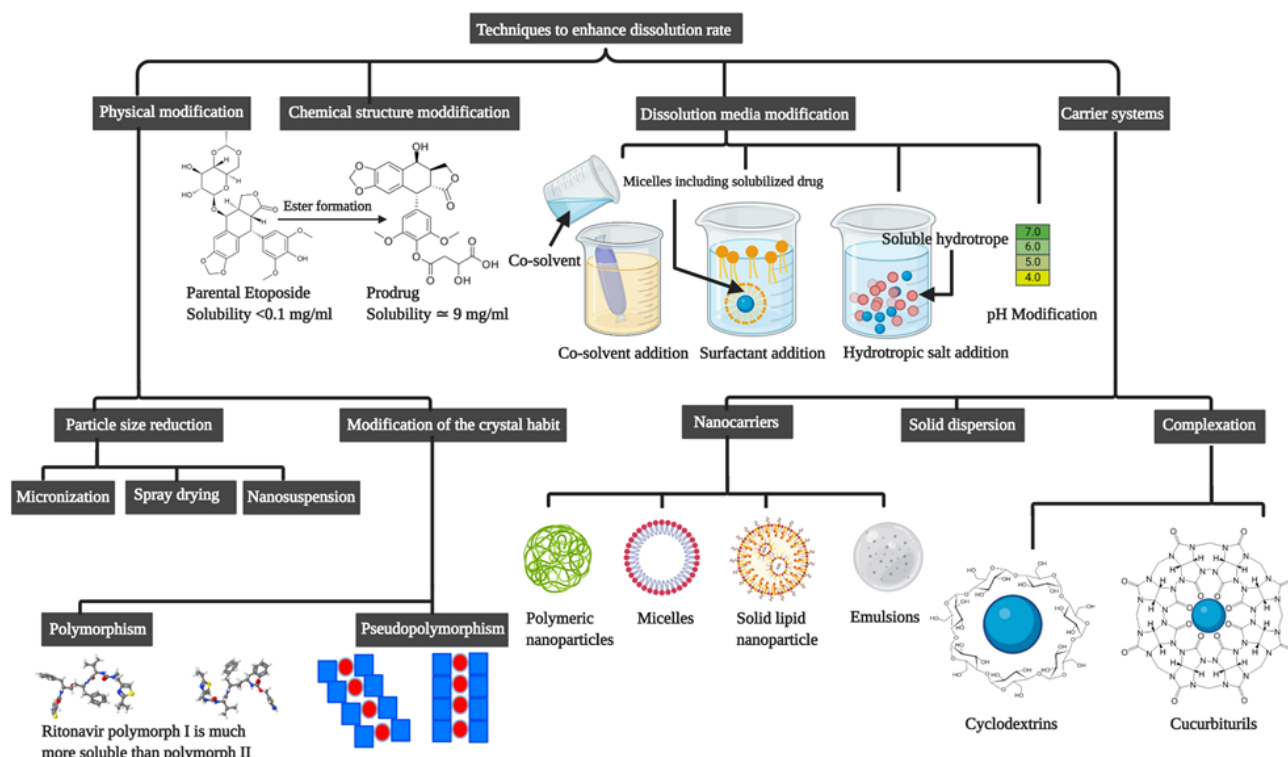


Figure 1: Enhancement strategies for drug solubility and dissolution rate.

in Figure 4. The application and limitations of these techniques are summarized in Table 2.

### Kneading method

The carrier is co-crushed with the drug forming a dense paste by using a minimal amount of organic solvents such as alcohol, acetone, or water. The incorporated amount of solvent is then extracted via a vacuum oven and the produced mass is ground into a fine powder.<sup>34,35</sup> The kneading method is cost-effective but challenged by the remaining solvent residuals.<sup>36</sup>

### Co-Milling Method

The method of co-milling is the most straightforward process for SDs preparation. The drug and carrier are co-blended without solvent or heating for hours to produce a homogeneous solid.<sup>37</sup> This process can also reduce the size of drug particles and transform the substance into an amorphous form. It is assumed that low-temperature tends to produce an amorphous form of the drug, while milling above  $T_g$  can yield crystalline forms. However, its main drawback is forming a heterogeneous mixture with weak drug-polymer interactions and low physical stability.<sup>38</sup>

### Hot-Melt Methods (Fusion-Based Method)

Sekiguchi and Obi first introduced the melting or fusion process to provide a simple and economical preparation method. In this process, the combination of drug and hydrophilic carrier is directly heated until melting. The melted mixture is then rapidly cooled and solidified in an

ice bath with strict stirring. The final solid mass is then crushed to reduce the particle size to be incorporated homogeneously in a suitable dosage form.<sup>39</sup> The melting point of this binary system depends on its composition, carrier selection and the weight fraction of the drug in the system. For example, poloxamer ( $P_{188}$ ) has a low melting point making it a suitable candidate for the fusion method.<sup>40,41</sup> The fusion method is limited by the thermal stability of the ingredients and their miscibility since some carriers have a melting point above the drug degradation temperature.<sup>42</sup>

The fusion method can be easily applied in laboratories using a conventional or microwave oven. Microwaves with frequencies of 0.3-300 GHz can be applied for the production of SDs. These waves pass through the drug/carrier mixture, making it oscillate in alignment with the externally applied radiations, thus generating heat enough for fusion.<sup>43</sup> This method is cost-effective and the heat is generated rapidly and uniformly.<sup>36</sup>

Two large-scale methods have been developed with the concept of fusion technique, including hot-melt extrusion<sup>42,44</sup> and KinetiSol<sup>®</sup>.<sup>45,46</sup>

Recently, the technology of using hot twin-screw extruders has provided a suitable choice to solve the scale-up problem of the fusion method. After feeding with the drug/carrier mixture, it is melted, mixed and squeezed between five different temperature zones reaching 185°C, then extruded through the die in various forms, including pellets, sticks and sheets.<sup>47,48</sup> Although this method usually uses high temperature and requires

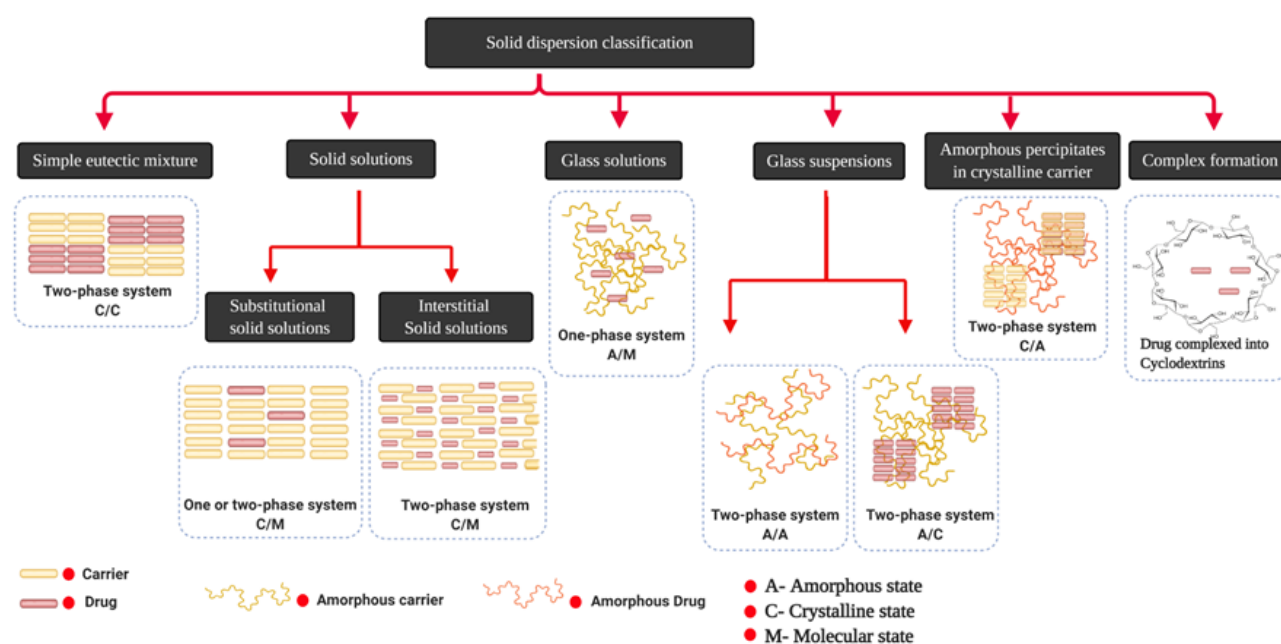


Figure 2: Classification of solid dispersion according to the physical state of the drug and carrier.



**Table 2: Applications of the solid dispersion preparation techniques and their advantages and limitation.**

Method	Carrier/Drug	Advantages	Limitations	Ref
<b>1. Kneading</b>	Poloxamer P <sub>188</sub> and 407/Boswellic acid	<ul style="list-style-type: none"> <li>A simple and economical method.</li> </ul>	<ul style="list-style-type: none"> <li>Heterogeneity</li> <li>Solvent residuals</li> </ul>	34,36
<b>2. Co-milling (comminution)</b>	$\alpha$ -Lactose / Budesonide	<ul style="list-style-type: none"> <li>A simple and economical method</li> </ul>	<ul style="list-style-type: none"> <li>Thermodynamic instability</li> <li>Alteration of the particle size distribution</li> </ul>	37,38
<b>3. Fusion</b>		<ul style="list-style-type: none"> <li>Solvent-free method</li> </ul>	<ul style="list-style-type: none"> <li>Require drug/carrier miscibility</li> <li>Thermolabile drugs</li> </ul>	
i. Simple fusion	Urea/Rofecoxib PEG 4000/Gliclazide	<ul style="list-style-type: none"> <li>A simple and economical method</li> </ul>	<ul style="list-style-type: none"> <li>Phase separation</li> <li>Scale-up</li> </ul>	5,89,90
ii. Hot-melt extrusion	Soluplus®/Telmisartan	<ul style="list-style-type: none"> <li>Continuous process suitable for large scale</li> <li>Short heating time</li> </ul>	<ul style="list-style-type: none"> <li>Processes at a high temp</li> <li>High input energy</li> <li>High shear force</li> </ul>	47,91,92
iii. Microwave induced fusion	PEG 6000 / Atorvastatin	<ul style="list-style-type: none"> <li>A rapid, uniform heating</li> <li>Short heating time</li> <li>Cost-effective</li> </ul>	<ul style="list-style-type: none"> <li>Scale-up</li> </ul>	36,93
iv. KinetiSol®	Polyvinyl alcohol/ Ritonavir	<ul style="list-style-type: none"> <li>Processes at a lower temp</li> <li>Processing thermolabile drugs</li> <li>Semi-continuous with output 1000 kg/hr.</li> </ul>	<ul style="list-style-type: none"> <li>N/A</li> </ul>	12,42,45
<b>4. Solvent evaporation</b>		<ul style="list-style-type: none"> <li>No heating</li> <li>Suitable for thermolabile drugs</li> </ul>	<ul style="list-style-type: none"> <li>Presence of toxic solvent residuals and high risk of phase separation</li> </ul>	5
i. Simple solvent evaporation	Phospholipid complex or TPGS 1000 or SiO <sub>2</sub> /Berberine	<ul style="list-style-type: none"> <li>Simple</li> <li>Suitable for heat-labile ingredients</li> </ul>	<ul style="list-style-type: none"> <li>High cost</li> <li>Phase separation may occur under slow evaporation condition</li> </ul>	94
ii. Spray drying	Mannitol/Diazepam	<ul style="list-style-type: none"> <li>Particle size control</li> <li>Fair powder flowability</li> <li>A rapid and economical method</li> <li>Scale-up.</li> </ul>	<ul style="list-style-type: none"> <li>Require high solubility of the drug/carrier mixture in the organic solvents</li> </ul>	54
iii. Lyophilization	Skimmed milk/ Simvastatin	<ul style="list-style-type: none"> <li>Homogeneity</li> </ul>	<ul style="list-style-type: none"> <li>High cost</li> </ul>	95
iv. Electrostatic spinning	PVP VA64/ Itraconazole	<ul style="list-style-type: none"> <li>High surface area for evaporation</li> </ul>	<ul style="list-style-type: none"> <li>Scale-up</li> </ul>	55
v. Fluid-bed coating	PEG 6000/resveratrol	<ul style="list-style-type: none"> <li>Suitable for tableting and encapsulation</li> <li>Higher drug loading</li> <li>Scale-up</li> </ul>	<ul style="list-style-type: none"> <li>Tedious process</li> </ul>	36,80
<b>5. Miscellaneous solvent-based methods</b>				
i. Solvent-melt	Polyoxyethylene 40 stearate/ cyclosporin	<ul style="list-style-type: none"> <li>Suitable for thermolabile components</li> </ul>	<ul style="list-style-type: none"> <li>Applicable for low dose drug</li> <li>Solvent traces may exist in the final product.</li> </ul>	85,86
ii. Supercritical Co <sub>2</sub>	PVP K30/ Carbamazepine	<ul style="list-style-type: none"> <li>Solvent-free</li> <li>Better flowability</li> </ul>	<ul style="list-style-type: none"> <li>Scale-up</li> </ul>	96
iii. Co-precipitation	CaCO <sub>3</sub> / Calcium carbonate	<ul style="list-style-type: none"> <li>Allow using less volatile solvents</li> <li>Permit reuse of the solvent</li> </ul>	<ul style="list-style-type: none"> <li>Plasticizer effect</li> <li>Presence of a large amount of adsorbed water</li> </ul>	5,97

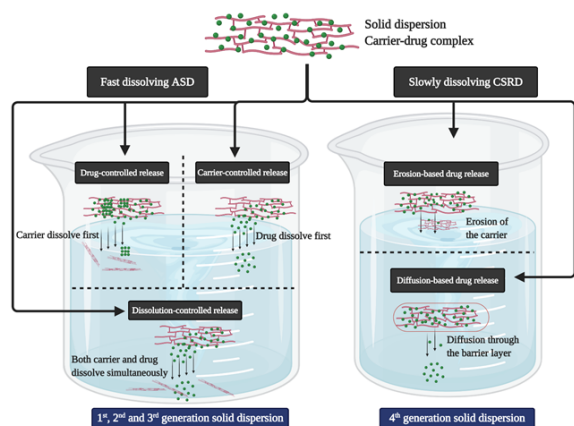


Figure 3: Mechanisms of drug release from a solid dispersion.

high shear force and input energy, the exposure time is too short, approximately one min.<sup>36,49,50</sup>

The method of KinetiSol<sup>®</sup> was introduced to the field of the pharmaceutical industry as an external heat-free fusion process. In this process, the fusion is based on the frictional forces resulting from exposure to high-speed rotating blades, as shown in Figure 5. The high shear quenching force is enough to melt the mixture without heat application; thus, it is used to prepare ASD in a large scale for heat-labile drugs.<sup>51</sup>

### Solvent Evaporation Methods

Solvent evaporation (SE) methods are available and widely utilized either in small labs or large-scale industries. The main procedure involves using a volatile solvent to dissolve the drug and carrier until attaining a homogenous mixture.<sup>52</sup> After that, to obtain SD, the incorporated amount of solvent is evaporated under different conditions under ambient, heating, or even freezing conditions. The choice of evaporation technique is dependent on the stability of each ingredient. Besides, the surfactant concentration is critical since the evaporation process gradually generates a diffusion layer that can retard drug release. Also, the evaporation speed, the type of solvent or co-solvent and the applied evaporation technique can significantly affect the yield homogeneity; it was reported by Hu *et al.* that the homogeneity was much higher when they used a rotary vacuum evaporator.<sup>5,53</sup> The SE technique is widely employed mainly to overcome drug instability issues when exposed to thermal stress since no or gentle heating is applied in this method. SE can be operated through scale-up techniques with an efficient output, including spray-drying,<sup>54</sup> freeze-drying, high-speed electrospinning.<sup>55</sup> While stirring hot plate, rotary evaporation,<sup>46</sup> Single-needle electrospinning<sup>55</sup> and lab spray-drying suitable as a small-scale methods.

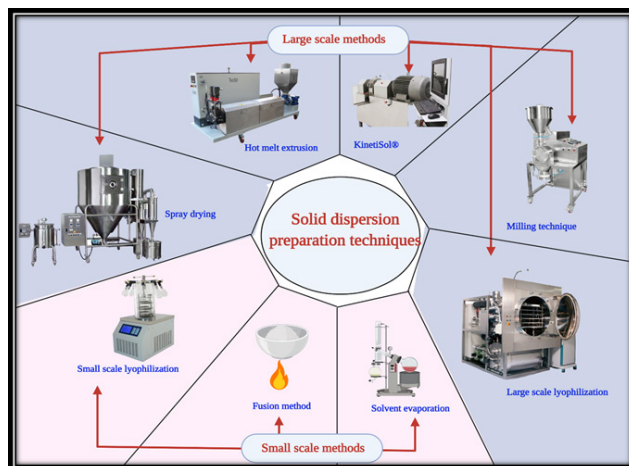


Figure 4: Classification of solid dispersion preparation techniques according to scalability.

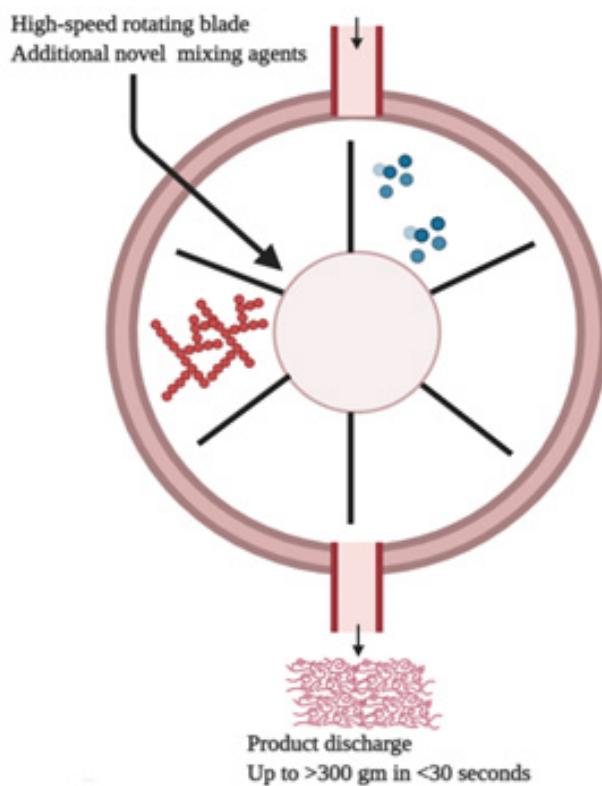


Figure 5: Diagrammatic presentation for the KinetiSol<sup>®</sup> process.

The high pressure utilized in the spray-drying technique causes evaporation by atomizing the solution via an adjusted diameter nozzle into a drying container.<sup>13,56</sup> The atomized particles have minimal size and large area, so evaporation becomes faster than typical methods. The quicker the drying process, the more homogenous product obtained since the heterogeneity encountered in common preparation approaches is avoided, yielding reproducible products. Moreover, the atomization

process controls the particle size of the produced dispersion. Controlling the particle size helps enhance the powder flowability by producing particles in a size range at which they cannot adhere together or produce clumps.<sup>57-60</sup>

The electrostatic spinning process is achieved by charging the polymer solution or melt stream electrostatically under the effect strong electric field.<sup>61</sup> The applied electrical acceleration and the high surface area provided by this method cause instant evaporation; thus, the product falls out as solid fibers.<sup>62,63</sup> Several trials were done to merge the electrospinning with other available techniques involving introducing mechanical forces<sup>64,65</sup> or thermal energy<sup>66,67</sup> to the conventional electrospinning process. In the electrospinning, the collector has different types, such as in Figure 6 it shows the traditional type of solid collector, while in Figure 7 it presents various types of radial collectors, which can be either rotating mandrel, rotating wire drum, or rotating disk.<sup>68,69</sup>

In this method, the power of the applied electrical field, temperature and flow rate are crucial factors for

controlling the product size and shape.<sup>70,71</sup> As seen in Figure 7, the electrospinning process is dependent on the polymer concentration since by increasing the polymer in the precursor solution; it starts to form homogenous fibers. In the case of low concentrated solutions, the product is composed of electrospayed fine powder, then begins to form beads precipitated on fibrous structure with increasing the concentration, then finally forming fibers with the highly concentrated precursors.<sup>72,73</sup>

In the freeze-drying technique, the drug is not exposed to any heating process since it is carried out by immersion under a freezing environment. The applied negative pressure to the solution -usually containing water- is responsible for the subsequent sublimation process.<sup>74</sup> The lyophilization process can be employed using spray freeze-drying<sup>75</sup> or ultra-rapid freezing.<sup>76,77</sup> The lyophilization speed and maintaining the temperature under Tg of the ingredients during sublimation have a pivotal role in controlling the phase separation.<sup>5</sup> Thus,

**Table 3: Classification of carriers used in solid dispersion and their pros and cons.**

Carrier Class	Chemical nature	Pros	Cons	Ref
Low molecular weight carriers	Saccharides (Sucrose- Glucose - Lactose)	<ul style="list-style-type: none"> <li>Masking the bad taste (sweetening effect)</li> </ul>	<ul style="list-style-type: none"> <li>Can compete with drug uptake</li> <li>Hereditary problems of intolerance</li> </ul>	98–100
	Organic acids (Citric acid - Tartaric acid)	<ul style="list-style-type: none"> <li>Applicable in preparing effervescent dispersion</li> </ul>	<ul style="list-style-type: none"> <li>Not practical for acid-sensitive drugs</li> </ul>	101
	Sugar alcohols (Mannitol- Sorbitol)	<ul style="list-style-type: none"> <li>Masking the bad taste</li> <li>Candidate for chewable tablet</li> </ul>	<ul style="list-style-type: none"> <li>Weak drug absorption enhancement</li> <li>Mannitol is not economical</li> <li>Remains unabsorbed in the gut exerting a laxative effect</li> </ul>	100,102,103
Large molecular weight (Polymeric carriers)	Polyethylene glycols (PEG 4000 and 6000)	<ul style="list-style-type: none"> <li>Excellent dispersibility</li> <li>Solubility enhancement</li> <li>Recrystallization inhibition</li> </ul>	<ul style="list-style-type: none"> <li>Hygroscopicity</li> <li>Oxidation and thermal degradation upon heating</li> <li>Potential irritant</li> </ul>	104,105
	Polyvidone (PVP K15 and K30)	<ul style="list-style-type: none"> <li>Excellent dispersibility</li> <li>Inhibits recrystallization</li> </ul>	<ul style="list-style-type: none"> <li>High viscosity</li> <li>Hygroscopicity</li> </ul>	106
	Cellulose derivatives (HPMC, HPC, and MC)	<ul style="list-style-type: none"> <li>Excellent dispersibility</li> <li>low hygroscopicity.</li> <li>Inert and safe</li> </ul>	<ul style="list-style-type: none"> <li>Some grades are of high viscosity with controlled release properties</li> <li>Incompatible with oxidizing agents</li> </ul>	107,108
	Carboxypolymethylene (Carbopol 907, 947 and 971)	<ul style="list-style-type: none"> <li>Ionic polymer excellent for co-precipitation technique</li> </ul>	<ul style="list-style-type: none"> <li>Some grades are potentially toxic and irritant</li> <li>Careful preparation to avoid forming clumps</li> </ul>	105,109
Functionalized polymeric carriers	Novel polymeric carrier (Soluplus®)	<ul style="list-style-type: none"> <li>Applicable using hot-melt extrusion technique</li> </ul>	<ul style="list-style-type: none"> <li>High viscosity</li> <li>High-melting point</li> </ul>	110
	Fatty acid macroglycerides (Gelucire 44/14 and Gelucire 50/13)	<ul style="list-style-type: none"> <li>Suitable for fusion method</li> <li>Carrier for oxidizable and light-sensitive drugs</li> </ul>	<ul style="list-style-type: none"> <li>Monolithic Gelucire 44/14 structures may sustain the drug release</li> </ul>	111–113

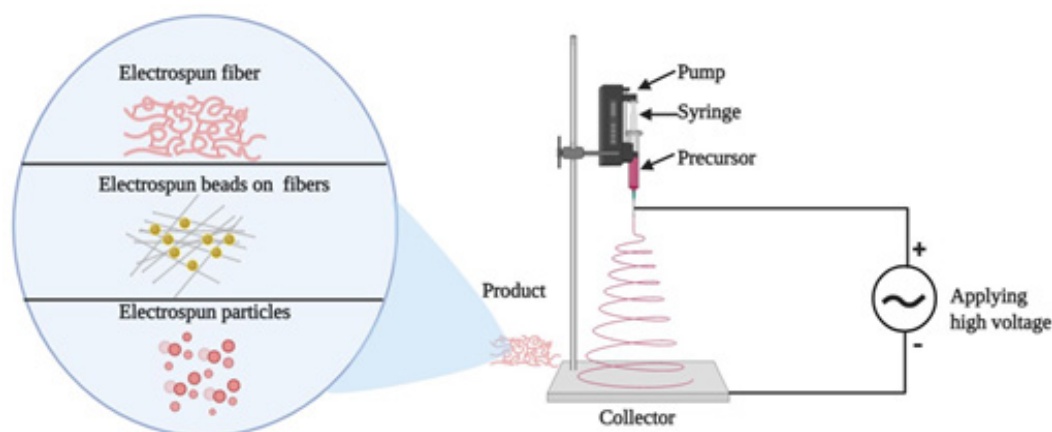


Figure 6: Diagrammatic presentation for electrospinning process and the formed product.

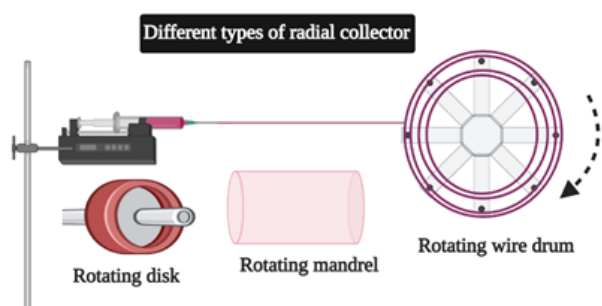


Figure 7: Diagrammatic presentation for the different types of radial collectors.

choosing the technique of freeze-drying is critical in the preparation of stable SD formulation.

The fluid bed coating was recently introduced as an effective technique that involves loading the drug/carrier mixture on inactive pellets evaporated by flowing air.<sup>78,79</sup> This method can be industrially employed since it is readily flowable for encapsulation and tableting.<sup>80</sup>

## Miscellaneous solvent-based methods

### Co-precipitation technique

The co-precipitation method is an alternate approach to the SE process using spray dryers, which is based on the concurrent precipitation of the dissolved components by the addition of anti-solvent.<sup>81</sup> The resulting precipitate is filtered and then washed to prevent the appearance of solvent residuals. To achieve a more homogenous product, simultaneous co-precipitation should be attained. The concurrent precipitation process is more responsive while using ionic polymers with pH-dependent solubilities such as ionic polymers; these polymers are mainly polymethacrylates and carbopols® products.

### Supercritical fluids

Carbon dioxide (CO<sub>2</sub>) was often documented as an alternative to the common solvents. Carbon dioxide

Table 4: Examples of natural carriers and their preparation methods.

Natural carrier	Drug	Preparation method	Reference
Alginate	Lovastatin & Indomethacin	Solvent evaporation	114
	Tanshinone IIA	Co-precipitation (Alcohol precipitation process)	115
Low molecular weight Chitosan	Indomethacin	Kneading	116
Skimmed milk	Simvastatin	Lyophilization	95
	Meloxicam	Rotary vacuum evaporation	117
Neem gum	Atorvastatin	Solvent evaporation and kneading	118
	Aceclofenac	Solvent evaporation and co-milling	119
Tamarind seed polysaccharide	Celecoxib	Kneading and Co-milling	120



as a supercritical fluid is desirable since it combines the high diffusivity and low viscosity of the gas and liquid density.<sup>82</sup> Initially, the drug/carrier mixture is solubilized in the supercritical CO<sub>2</sub> and sprayed via a nozzle into the expansion vessel. The sprayed particles are rapidly forming SD of the target size. When CO<sub>2</sub> is used as an anti-solvent, the drug/carrier mixture is introduced in an organic solvent. After expelling the mixture into the vessel, the organic solvent is rapidly removed by supercritical CO<sub>2</sub>, forming SD particles.<sup>83,84</sup>

### Melting-Solvent Evaporation Methods

This method is a combined approach involving fusion and SE techniques. Once the drug solution is prepared, it is then added to the carrier in a molten state with gentle mixing forming a homogenous mixture. After that, the solvent is evaporated at a lower temperature to obtain a consistent solid product.<sup>85,86</sup>

### Carriers in solid dispersion

Carriers used to produce SDs have a pivotal role in controlling the drug release since they can enhance or retard the drug dissolution, whether achieved through diffusion or dissolution-based mechanism, as previously mentioned.<sup>17,25,87</sup>

A drug carrier should have fair solubility in various solvents, specifically in water and lacking toxicological and pharmacological effects. Chemically, the carrier should have thermal stability and compatibility with the formulated drug.<sup>17</sup>

Carriers are classified according to their molecular weight into low molecular weight and polymeric carriers of high molecular weight, in addition to the functionalized polymeric carriers, as shown in Table 3.

Recently, carriers derived from natural origin have gained great interest and became favorable over synthetic carriers because they are biocompatible, available, chemically inert and biodegradable.<sup>17</sup> Natural carriers that has enhanced the dissolution rate and bioavailability of model drugs were presented in Table 4.

However, many limitations have been accompanied by natural carriers' use, including the uncontrolled hydration rate, viscosity changes and microbial contamination. The first limitation can be overcome chemically by carboxymethylation or carbomoyl ethylation of active carboxyl or hydroxyl group resulting in increased water solubility. Also, the latter limitations can be physically treated through dry heating.<sup>17,88</sup>

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### ABBREVIATIONS

**SD:** Solid Dispersion; **SE:** Solvent Evaporation; **BSCS:** Biopharmaceutical Classification System; **PVP:** PolyVinyl Pyrrolidone; **PEG:** Poly Ethylene Glycol; **HPC:** Hydroxy Propyl Cellulose; **MC:** Methyl Cellulose; **HPMC:** Hydroxy Propyl Methyl Cellulose; **T<sub>g</sub>:** Transition glass temperature; **ASD:** Amorphous Solid Dispersion; **CRSD:** Controlled Release Solid Dispersions; **FDT:** Fast dissolving tablet.

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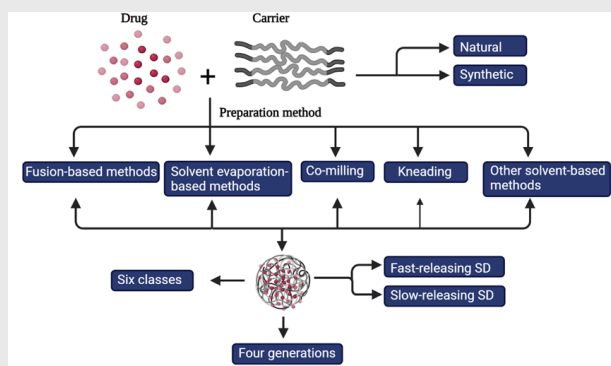
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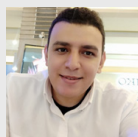
## PICTORIAL ABSTRACT



## SUMMARY

- Many of the currently marketed drugs suffer from poor water solubility and decreased oral bioavailability.
- Several pharmaceutical strategies were proposed, including solid dispersion as a straightforward technique to overcome the addressed issue of poor water solubility.
- The first part of the review discusses the classification of solid dispersion according to their recent advances and the nature of drug dispersion into the carrier
- The second part focused on the available preparation methods and their development in the up-to-date literature.
- The last part covered the different classes of solid dispersion carriers, including synthetic and natural ones.

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