Expert Opinion

Improved dissolution behavior of lipophilic drugs by solid dispersions: the production process as starting point for formulation considerations

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Introduction: Many new drug substances have low aqueous solubility which can cause poor bioavailability after oral administration. The application of solid dispersions is a useful method to increase the dissolution rate of these drugs and thereby improve their bioavailability. So far, several methods have been developed to prepare solid dispersions. To obtain a product with the desired attributes, both the formulation and production processes should be considered.

Areas covered: The most currently used methods to produce solid dispersions, such as the fusion method, hot melt extrusion, spray drying, freeze drying and supercritical fluid precipitation, are reviewed in this paper. In addition, the physicochemical characteristics of the obtained solid dispersions are discussed.

Expert opinion: Solid dispersions can be successfully prepared by simple fusion, hot melt extrusion, spray drying, freeze drying and supercritical fluid precipitation. Hot melt extrusion, spray drying and freeze drying are processes that can be applied for large scale production. The simple fusion method is not very suitable for large scale production, but is particularly suitable for screening formulations. The most recent method to produce sold dispersions is supercritical fluid precipitation. The process conditions of this method need extensive investigation, in particular in relationship with the selection of the type of carrier and/or solvent. Both processes and formulation aspects strongly affect the characteristics of solid dispersion products. Furthermore, application of crystalline solid dispersions is gaining increasing interest because they are thermodynamically more stable than amorphous solid dispersions.

Keywords: dissolution, oral dosage form, poorly water-soluble drugs, solid dispersion

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1. Introduction

Bioavailability refers to the extent and rate at which a drug reaches the systemic circulation after administration. When the drug is administered via the intravenous route, the bioavailability is considered to be 100%. However, most of the drugs are administered via other routes, such as the oral route; due to poor dissolution, the incapability to permeate the absorbing membrane or metabolic transformation during the absorption process, the bioavailability of these drugs is often incomplete. Several drugs yield erratic absorption after oral administration caused by incomplete dissolution in the gastrointestinal (GI) lumen when administered in a solid dosage form.

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Article highlights.

- Fusion is the simplest method to produce solid dispersion and is, therefore, useful for screening formulations.
- Hot melt extrusion is a promising method. The method can be applied to various drugs. Application of synthetic polymers as carriers in solid dispersions is preferred for this method.
- Spray drying and freeze drying are frequently applied methods to produce solid dispersions. The type of solvents used strongly influences the characteristics of the final solid dispersions such as powder morphology, physical state of the component in the solid dispersion and dissolution rate of the drug.
- Supercritical fluid precipitation is a more recent method to prepare solid dispersions. The solubility of drug and carrier in the supercritical fluids, and the miscibility of solvent and supercritical fluids are the key factors in the production process.
- The physical state of the components in solid dispersions and dissolution rate are determined by the production method, the process conditions, the type of carriers and the drug load.

This box summarizes key points contained in the article.

The Biopharmaceutics Classification System (BCS) is used for correlating *in vitro* drug dissolution and *in vivo* bioavailability following oral administration. Solubility and permeability (including metabolic transformation) of drugs are essential parameters determining bioavailability. Consequently, drugs can be classified into four groups as shown in **Table 1** [1]. BCS class II drugs are of specific interest because the number of poorly water-soluble compounds rapidly increases in drug discovery [2]. Permeability of BCS class II drugs over the intestinal membrane is fast and hence the absorption will mainly be determined by the dissolution rate of the drug in the GI fluids. Therefore, ways to enhance the dissolution rate of poorly water-soluble drugs becomes a challenge. Application of solid dispersions is an approach which has been used to enhance the dissolution rate of these drugs. Solid dispersions are generally systems in which the drug is incorporated in an inert hydrophilic carrier. The solid state of drugs in the solid dispersions can be amorphous and/or crystalline. When the drug is in the amorphous state, it can be incorporated in the solid dispersion as particles or dispersed over the carrier at a molecular level. However, when the drug is in the crystalline state, it is incorporated as particles only. Theoretically, the drug could form mixed crystals with the carrier. However, to our knowledge, such mixed crystals have never been encountered with solid dispersions. When the drug is incorporated in the solid dispersion as particles, the size of these particles is usually in the nano-sized range [3,4]. The very small particles result in an increased dissolution rate which can be explained by the Noyes-Whitney equation [5]:

$$\frac{dm}{dt} = \frac{D * A}{h}(C_s - C_{bulk}) \quad (1)$$

where dm/dt is the dissolution rate of drug, D is the diffusion coefficient of drug, A is the surface area of the drug, C_s is the saturation concentration of the drug, C_{bulk} is the concentration of drug in the bulk and h is the thickness of the hydrodynamic boundary layer.

The very small particle size results in a large surface area (A) and thus in an increased dissolution rate. In addition, very small (nano-sized) particles not only result in a large surface area (A) but also in an increased saturation concentration (C_s) which can be derived from the Ostwald-Freundlich equation [6]:

$$C_{s,curve} = C_{s,flat} * \exp\left(\frac{2 * \gamma * M}{R * T * \rho * r}\right) \quad (2)$$

where $C_{s,curve}$ is the saturation concentration at a curved surface, $C_{s,flat}$ is the saturation concentration at a flat surface, γ is interfacial surface tension of the solid drug to solution interface, M is the molecular mass of drug, R is the gas constant, T is the temperature, ρ is the density of drug and, finally, r is the radius of curvature of the dissolving surface. The decreased radius of the curvature of the dissolving surface (r) results in the increased saturation concentration at the curved surface ($C_{s,curve}$) and thereby in an increased dissolution rate.

Moreover, the very small particle also results in a decreased thickness of the hydrodynamic boundary layer (h) in Equation (1) which can be explained by the Prandtl boundary layer equation [7]:

$$h = k * \frac{\sqrt{L}}{\sqrt{V}} \quad (3)$$

where h is the thickness of hydrodynamic boundary layer, k is a constant, L is the length of the surface in the direction of flow and V is the relative velocity of the flowing liquid versus the flat surface. The decreased particle size results in a decreased length of the surface in the direction of flow (L) and thus in a decreased thickness of hydrodynamic boundary layer (h). In Equation (1), the decrease in the thickness of hydrodynamic boundary layer (h) yields an increased dissolution rate.

In addition, when the drug is incorporated in the amorphous state, it has a higher apparent solubility (C_s) than when the drug is crystalline which results in a higher dissolution rate [8]. Finally, as the drug in the solid dispersion is in intimate contact with the hydrophilic carrier, its wetability is improved resulting in an increased dissolution rate [9].

An alternative way of thinking describes the mechanism of dissolution of solid dispersions as either carrier- or drug-controlled dissolution [10]. The type of the mechanism depends on the drug load. For both mechanisms, a concentrated carrier-layer is formed at the dissolving surface in which the drug has to pass through. However, the difference is that in case of the carrier-controlled dissolution, the drug dissolves into the concentrated carrier-layer and then diffuses as dissolved molecules into the bulk of the dissolution medium.

Table 1. Biopharmaceutics classification system.

Class	Solubility	Permeability	Examples of drugs
I	High	High	Cyclophosphamide, pyrazinamide, stavudine, zidovudine
II	Low	High	Dapsone, griseofulvin, phenytoin, nifedipine
III	High	Low	Atenolol, colchicine, cimetidine, hydrochlorothiazide
IV	Low	Low	Furosemide, indinavir, saquinavir, ritonavir

This situation occurs when the drug is incorporated in the carrier at a relatively low load. The physicochemical properties of carrier, for example, the molecular mass and the viscosity, determine the dissolution behavior of the drug from the solid dispersion. On the other hand, in case of the drug-controlled dissolution, the drug does not dissolve in the concentrated carrier-layer but diffuses as particles through this layer and these particles subsequently dissolve in the bulk of the dissolution medium. This situation occurs when the drug is incorporated in the carrier a relatively high drug load. The physicochemical properties of drug, especially the particle size of drug, play a major role on the dissolution rate of solid dispersion.

Most solid dispersions exist as glass solutions, glass suspensions or fully crystalline dispersions. A glass solution is a system in which the drug is dispersed in an amorphous carrier on a molecular level. However, because the amorphous state has a higher Gibbs energy than the crystalline state, a glass solution is thermodynamically unstable. Consequently, both drug and carrier may be prone to crystallization during storage. A change of the physical state of drug and/or carrier is highly unwanted as it may affect the dissolution behavior of the solid dispersions. Hydrophilic carriers with a high glass transition temperature (T_g) are used in order to improve the stability of the glass solutions. Examples of carriers with a high T_g are polyvinylpyrrolidone (PVP) [11,12] or hydroxypropyl methylcellulose (HPMC) [13,14] and inulin [15]. In general, it is rather difficult to prepare glass solutions with a high drug load without the formation of drug clusters, which may limit the application of this system to low-dosed drugs.

A glass suspension can be described as a system in which a drug is dispersed as amorphous clusters in an amorphous carrier. Usually, the drug is also partially dispersed in the carrier at a molecular level. This type of solid dispersion is usually found when the drug load is high. For example, it has been found that diazepam incorporated in inulin solid dispersions at a drug load of 35% w/w partially existed as amorphous clusters and was partially dispersed in the carrier at a molecular level [15]. A disadvantage of a glass suspension is that after processing and/or after storage, the drug in the amorphous clusters may be prone to crystallization, in particular when the drug has a low T_g. For instance, it has been found that fenofibrate (T_g = -20°C) incorporated in PVP, inulin or hydroxypropyl-β-cyclodextrin (HPβCD) at a drug load of 50% w/w was partially crystalline and partially in the amorphous state [16].

A fully crystalline dispersion is a system in which small drug crystals are intimately dispersed in a crystalline carrier. Because the drug is in the crystalline state, its physical stability is better than its amorphous counterpart. However, the solubility and dissolution rate of drug in crystalline state are lower than that in the amorphous state. In order to still maintain a fast dissolution rate, the preparation of fully crystalline dispersions containing nano-sized drug particles has become a fascinating challenge. For example, a crystalline dispersion of fenofibrate incorporated in PEG 8000 was investigated. Both fenofibrate and PEG readily crystallize because of their very low T_g values. The particle size of fenofibrate in PEG was < 10 μm whereas particle size of unprocessed fenofibrate was 100 μm [17]. Other drug substances dispersed in PEG in the crystalline state that have been reported are, for example, ibuprofen [18], ofloxacin [19], nifedipine [20] and flurbiprofen [21].

The type of solid dispersion and its dissolution behavior are strongly influenced by the physicochemical properties of drug and carrier and the used production process. This review focuses on techniques widely used for preparing solid dispersions (thermal and solvent methods). Furthermore, process and formulation aspects affecting the type of solid dispersion that is obtained are described. In addition, critical concerns and advantages/disadvantages of the methods are discussed.

2. Thermal method for the production of solid dispersions

2.1 Simple fusion

The fusion method refers to a process in which a drug is dissolved in one or more molten carriers or carriers in the rubbery state and then cooled under stirring to form a solid dispersion. Alternatively, the drug is first dissolved in a solvent and then transferred into a molten carrier. Subsequently, the solvent is evaporated by heat. After solidification, the solid mass is milled, extruded and/or sieved in order to obtain a powder. Sekiguchi and Obi were the first to use this technique for preparing a solid dispersion (which was composed of sulfathiazole incorporated in urea) [22]. The fusion method is a very simple process. It may be useful for screening of formulations. Nevertheless, one major disadvantage of this method is that the texture of the solid dispersion after cooling is quite hard. Therefore, size reduction of the solid dispersion may be difficult. Factors that can influence dissolution behavior of drug are the type of carrier, the cooling rate and the final temperature.

The most important requirement with this method is that drug and carrier should be stable at the process temperature. In general, carriers should have a lower melting point (T_m)

or T_g than the drug to allow a more practically processing temperature and decrease the potential of drug degradation. Many carriers have been used such as mannitol, PEGs and poloxamers. PEGs are mostly used for this method because they have a low melting point of about 37 – 63°C, depending on its molecular mass. In addition, many drug substances dissolve quite well in molten PEG. Several drugs have been incorporated in PEG, resulting in either eutectic or monotectic mixtures [17,23-27]. The phase diagrams of a typical eutectic mixture and a monotectic mixture (e.g., a mixture of PEG and drug) are shown in **Figure 1A, B**. Both eutectic and monotectic mixtures are described as systems in which drug and PEG are miscible in liquid state; however, the system is immiscible in the solid state, existing as two crystalline phases of the pure components. The melting point of a eutectic mixture is below that of the pure drug and PEG whereas in the case of monotectic mixture, the melting point of PEG remains constant and is independent of the amount of drug. When a mixture of eutectic composition is cooled, both drug and carrier will crystallize simultaneously which facilitates the formation of small crystals. In contrast, when either drug or carrier starts to crystallize first, the chance to obtain large crystals is high. Therefore, the eutectic mixture is desirable because it yields small drug and carrier crystals resulting in an increased dissolution rate. Furthermore, a lower process temperature than the melting points of drug and carrier can be used for eutectic mixtures. A eutectic mixture of fenofibrate and PEG 8000 is formed at a drug load of about 20 – 25% w/w [28]. The particle size of fenofibrate in the eutectic mixture was > 10 times smaller than that of the unprocessed fenofibrate. In addition, it has been found that when fenofibrate [24] or naproxen [27] was incorporated in PEGs of various molecular mass, the dissolution rate of these drugs was independent on the molecular mass of PEG. It has also been found that these drugs did not interact with PEG. In contrast, it has been found that flurbiprofen did interact with PEGs and that the dissolution rate of solid dispersion of flurbiprofen in PEG increased with decreasing molecular mass of PEG. This result was attributed to the increased extent of interactions and increased solubilizing capacity of the carrier with decreasing molecular mass [24].

Poloxamers are nonionic surfactants composed of polyoxyethylene–polyoxypropylene–polyoxyethylene triblock copolymers. The two polyoxyethylene parts are hydrophilic whereas the polyoxypropylene part is hydrophobic. Poloxamers have a T_m of 52 – 57°C. Poloxamer 188 [29-32] and poloxamer 407 [33-35] have been used as carriers for various model drugs. These studies consistently reported that the state of the drugs was partly crystalline and partly amorphous. The observed increased dissolution rate of the drugs is most probably due to the decreased particle size, the reduced crystallinity of the drug and the surface-active property of poloxamer itself. Shah *et al.* prepared poloxamer 188-based solid dispersions containing rofecoxib at varying cooling temperatures and drug loads [36]. A decrease in cooling temperature and an increase in amount of poloxamer 188 resulted in an increased dissolution rate of drug, possibly due to higher proportion of amorphous rofecoxib in the solid dispersions. However, some studies found that an increase in the amount of poloxamer led to a decrease in drug dissolution rate because poloxamer at a high concentration forms a gel during dissolution [29,33].

Solid dispersions composed of a drug incorporated in a combination of PEG with other additives have also been investigated. The purposes of using additives are to increase miscibility of drug and carrier, increase the drug load, enhance the dissolution behavior of solid dispersions or improve the storage stability of solid dispersions. An example of such a third component are surfactants [19,37-49]. About < 3% w/w griseofulvin completely dissolved in molten PEG 6000. Interestingly, when 2% w/w sodium dodecyl sulfate was incorporated in the binary mixtures, griseofulvin could be dissolved in molten PEG 6000 up to a drug load of 40% w/w, indicating that the surfactant increased the miscibility of the components [44]. PEG is a semi-crystalline carrier which contains both crystalline and amorphous components [50]. Wulff *et al.* and Alden *et al.* have prepared micelles with lipophilic drugs incorporated and mixed them in molten PEG [43,51]. After cooling, the micelles were incorporated in the amorphous fraction of PEG. Dissolution behavior of ternary dispersions containing drug, PEG and surfactant was significantly improved as compared to the dispersions without surfactant. Also, the type and amount of surfactant incorporated in the dispersions affect the dissolution behavior of drugs [38,41]. However, increasing the concentration surfactant to 10% w/w in the ternary dispersions did not give any further improved dissolution behavior of glyburide [37].

Polymers as a third component have also been incorporated in binary dispersions. A solid dispersion of nifedipine and PEG 1500 showed excellent dissolution behavior, but was unstable on storage. Combinations of the drug with PEG 1500 and PVP (K12 and K30), polyvinylpyrrolidone-co-vinylacetate (PVPVA 64) or Eudragit® EPO at a ratio of 1:1 were melted at 140°C allowing the formation of homogeneous mixtures. A superior dissolution behavior of nifedipine after storage was found with the combination of PEG 1500 and PVPVA 64, probably because of the low mobility of drug in PVPVA 64 and consequently a slow re-crystallization on contact with dissolution medium [52].

2.2 Hot melt extrusion

Hot melt extrusion is a combination of melting and a mechanical process in which the drug, polymer and optionally plasticizers are mixed and melted under controlled conditions of temperature and shear forces. The mass of co-melts is mixed with the help of the transport screws and extruded through a die plate, yielding solid dispersions. Extensive reviews on hot melt extrusion technology have been published previously [53-55]. One of the technologies based on hot melt

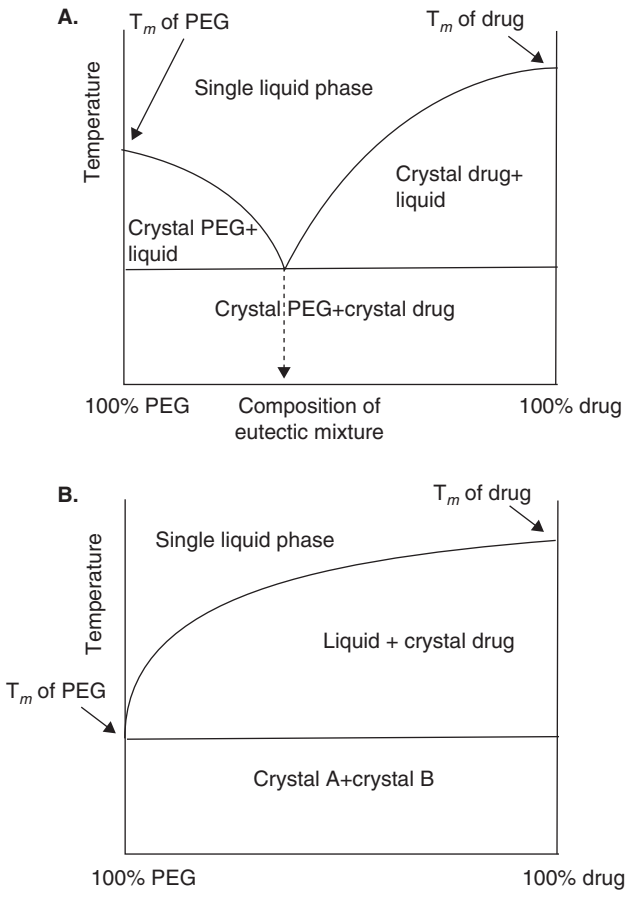

Figure 1. Phase diagrams of typical (**A**) eutectic mixture and (**B**) monotectic mixture (e.g., a mixture of PEG and drug).
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extrusions is the so-called Metrex® process which has been applied for the development of a ritonavir–lopinavir combination tablet with improved dissolution characteristics [56]. Another recently developed technology based on molten substances (a mixture of molten drug and carrier is sprayed on inert particulates) is called Meltdose®. This technology has been applied for the improved dissolution of fenofibrate [57].

The most important parameter for hot melt extrusion is the process temperature. The optimal process temperature is determined by the T_m of the drug, the T_m of the crystalline carrier, the T_g of the amorphous carrier and the thermoplastic properties of the carrier. During the extruding process, the drug should be thoroughly mixed with the carrier and both should not degrade at the process temperature. In general, the process temperature has to be higher than T_m or T_g of the carrier to soften and thereby decrease the viscosity of the carrier allowing sufficient flow through the extruder. Therefore, the T_m or the T_g of carrier should not be too high to limit the risk of drug degradation and/or to yield a practically process temperature.

Determination of the decomposition temperature of drug, carrier or mixture of drug and carrier is beneficial for setting the maximum process temperature [58]. Thermal gravimetric analysis is only useful if the substances change in weight during degradation. In addition, to screen the miscibility of the drug in the carrier, estimation of solubility parameters, thermal analysis, for example, by differential scanning calorimetry and hot stage microscopy are useful techniques [59-61]. Such investigations indicate the most suitable carrier for a specific drug. If the drug is miscible with the carrier, it has the potential to form a glass solution.

Carriers, which have been widely used with this method, can be divided into two categories, synthetic polymeric and carbohydrate carriers. Examples of synthetic polymeric carriers are PVP K30, PVPVA 64 and Eudragit® E100 (polymethacrylates). These polymers are amorphous in nature. In addition, they have the thermoplastic properties which are required for the extrusion process. Solid dispersions have successfully been prepared from these polymers. For example, tolbutamide, indomethacin, nifedipine or lacidipine has been incorporated in PVP K30 or PVPVA 64 at a drug load of 50% w/w. The extruder temperature was close to the T_m of drugs. It is concluded that glass solutions of these drugs and carriers can only be obtained if the drugs are completely dissolved in the rubbery/molten carrier and no phase separation occurs during the process (e.g., during the cooling of the product). Most solid dispersions showed improved dissolution rates as compared to their corresponding physical mixtures. In addition, all these solid dispersions remained stable during storage at 25°C/< 10% RH for 8 weeks. However, during storage at 25°C/75% RH, only the solid dispersions of indomethacin incorporated in PVP K30 or PVPVA 64 were stable. The differences in physical stability of the drugs/carriers are possibly due to the differences in degree of hydrogen bonding between drug and carrier [62]. In another study, fenofibrate was incorporated in PVPVA 64 or Eudragit® E100 at a drug load of 33% w/w. In these cases, no glass solutions were formed. Instead, the drug was incorporated in the carrier partially in the amorphous state and partially in the crystalline state. Dissolution of the solid dispersion with PVPVA 64 as carrier was slower than that with Eudragit® E100 as carrier due to gel formation of PVPVA 64 during dissolution. Interestingly, the bioavailability of Eudragit® E100 solid dispersion was superior to the marketed product fenofibrate capsules [63]. An increased bioavailability of a solid dispersion prepared by hot melt extrusion as compared with the marketed product was also found with a solid dispersion in which nimodipine was incorporated in PVPVA 64 [64].

Examples of carbohydrate carriers that are frequently used in solid dispersions prepared by hot melt extrusion are cyclodextrin (CD) derivatives and HPMC. The dissolution behavior of solid dispersions of ketoprofen incorporated in β-CD or sulfobuthyl ether-β-cyclodextrin (SBE_7βCD) at a drug load of 50% w/w was compared. The drug was

incorporated in the carriers predominantly in the crystalline state. Solid dispersion from $SBE_7\beta CD$ gave a higher dissolution rate than that from β-CD possibly because the drug interacts stronger with $SBE_7\beta CD$ than with β-CD during dissolution [65]; also, the surface active properties of the $SBE_7\beta CD$ may have played a role. In another study, a solid dispersion of itraconazole and HPMC 2910 at a drug load of 40% was prepared. The drug was amorphous in the carrier resulting in an increased dissolution rate as compared to the corresponding physical mixture. Furthermore, after storage for 6 months at 40°C/75% RH, the solid state of the drug and the drug content in the solid dispersion did not change [66].

Besides the carrier, additives are frequently used in the formulations in order to decrease the T_m or T_g of carriers and/or to facilitate the flow of the mixture through the extruder. This enables a reduction of the process temperature. Surfactants are the most used plasticizers in formulations for hot melt extrusion. They can interact with carriers resulting in increased chain mobility by which the T_m or T_g of carriers are decreased. For example, solid dispersions of a poorly soluble drug (name not specified) and the surfactant Tween® 80 incorporated in PVP K30 or HPMC E5 were investigated. It was found that the melt viscosity of all mixtures with Tween® 80 was lower than that of the corresponding mixtures without the surfactant. Furthermore, fully amorphous solid dispersions were obtained from both carriers [67]. However, probably due to their lowered T_g values, the solid dispersions showed limited storage stability as the drug partially crystallized in both cases during storage at 30°C/60% RH [68].

In addition to surfactants, other additives such as citric acid [69], methylparaben [70] or even the drug [65] can act as plasticizers. Interestingly, in another study, supercritical carbon dioxide (CO_2) was injected in the extrusion zone. It has been reported that the supercritical CO_2 was a temporary plasticizer for PVPVA 64, Eudragit® E100 or ethylcellulose, resulting in a decreased process temperature. In addition, the carriers showed after processing with the supercritical CO_2 a pore-structure resulting in an increased surface area and, therefore, an increased dissolution rate [71]. Other solid dispersions [72-83] prepared by hot melt extrusion are summarized in **Table 2**.

3. Solvent method for the production of solid dispersions

The major advantage of using a solvent for the preparation of solid dispersions is that it increases the capability of a drug to be incorporated in a carrier as a solution or suspension at mild temperatures and thereby avoids thermal degradation. Because this production process involves the application of solvents, various technologies for drying have been investigated.

3.1 Spray drying

Spray drying has been widely used for producing solid dispersions. The process mainly consists of atomization, drying (by heat) and powder collection. Samples to be spray dried can be a solution or a suspension, which normally contains a drug, a carrier and sometimes additives. The sample is atomized by feeding it through a nozzle, creating fine droplets. The solvent in these fine droplets is rapidly evaporated by hot air or an inert gas, yielding a dry powder. The final product is usually collected by a cyclone system. Spray drying is an efficient method to produce solid dispersions due to rapid evaporation of the solvent. The feed rate of the solution, the flow rate of the atomizing air, and the inlet temperature and flow rate of the drying gas are process settings that affect the morphology of the powder, product yield, physicochemical characteristics of the product and amount of residual solvent in the powder. Optimization of the process settings has been investigated in many studies [84-86]. Also, a model-based methodology for spray-drying process development has been described [87].

Organic solvents or co-solvents are used because of the poor aqueous solubility of many drugs. With a proper choice of solvent or co-solvent system, solutions with a relatively high solid content can be prepared by which an efficient process and a high production output can be achieved. Because the final product will often contain a certain amount of residual solvent(s), the use of toxic solvents should be avoided. Nevertheless, in many studies highly toxic solvents such as dichloromethane or chloroform have been used. Differences in evaporation rate of the solvents and solubility of solutes in the solvent or co-solvent system can influence the particle morphology. Rizi *et al.* prepared solid dispersions of hydrocortisone in Eudragit® L100 by varying ethanol:water ratios (100:0, 75:25 and 50:50) [88]. Spray drying with pure ethanol gave particles with a wrinkled surface whereas the use of ethanol–water co-solvent mixtures resulted in more spherical particles.

The procedures used to incorporate a drug in a carrier by spray drying can influence the solid state of drug in the final solid dispersion. For example, tacrolimus was incorporated in HPβCD and dioctyl sulfosuccinate (DOSS) by three different procedures. In the first procedure, the drug, HPβCD and DOSS were dissolved in a dichoromethane–ethanol mixture. In the second procedure, the drug and DOSS were dissolved whereas the carrier was dispersed in ethanol. And in the third procedure, HPβCD and DOSS were dissolved while the drug was dispersed in water. The two samples in which the drug was dissolved (first and second procedures) yielded solid dispersions with tacrolimus incorporated in the amorphous state. Obviously, the sample in which the drug was dispersed (third procedure) yielded a solid dispersion with tacrolimus incorporated in the crystalline state. The first procedure gave the highest dissolution rate of tacrolimus followed by the second procedure [89]. It is well known that CDs and lipophilic drugs can form inclusion complexes which readily dissolve. Obviously, such complexes can only be formed when both components are in the dissolved state. Therefore, only during the preparation of the solid dispersion

Table 2. Examples of solid dispersions prepared by hot melt extrusion.

Drug	Carrier	Plasticizer	Remarks	Ref.
Spironolactone	HPβCD	Sorbitol and corn starch	Corn starch was used to improve the thermoplastic property of the mixture. The process temperature could be decreased	[75]
Itraconazole	HPMC:HPβCD	–	Ratio between the two carriers was optimized to allow an efficient process. The optimized ratio of HPMC:HPβCD was 45:15	[82]
Itraconazole	Eudragit® L100-55:Carbopol® 974P	Triethyl citrate	Amorphous solid dispersion was obtained Carbopol® 974P was used in formulation to sustain the supersaturation concentration of the drug from Eudragit® L100-55 at neutral pH	[80]
Bicalutamide	PVP K25	–	At maximum drug load of 30% w/w, glass solutions were obtained. The amorphous solid dispersion was stable for 12 months at 20°C/40%RH	[72]
Indomethacin	Eudragit® EPO PVP K30 PVPVA 64 Poloxamer 188	–	Eudragit® EPO, PVP K30 or PVPVA 64 was miscible with the drug. In contrast, poloxamer 188 was partially miscible with the drug	[81]
Indomethacin	Eudragit® EPO PVP K30 PVPVA 64	–	After storage stability for 3 months at 40°C/75% RH, intrinsic dissolution rate of dispersions from Eudragit® EPO was superior to that from the other two carriers	[79]
Hydrocortisone	PVPVA 64 HPMC E3	–	PVPVA 64 allowed a lower process temperature than HPMC E3	[73]
Ritonavir	PVPVA 64:colloidal silicon dioxide	Sorbitan monolaurate	Ritonavir was amorphous in the carrier. Nano/micro particulates were obtained when the solid dispersion was dispersed in an aqueous medium	[76]
17β-Estradiol hemihydrate	PEG 6000 PVP K30 PVPVA 64	Sucroester® WE15 Gelucire® 44/14	Solid dispersions with PVP K30 and Sucroester® WE15 yielded a proper flowability of mixture and the fastest dissolution. The drug in this solid dispersion was partially crystalline	[83]
Celecoxib	Eudragit® EPO	–	Solid dispersion with a drug load of 50% w/w showed an improved dissolution rate. The solid dispersion was stable during storage for 6 months at 25°C/60%RH	[77]
Celecoxib	PVP K30	–	Introducing the supercritical CO_2 in the process yielded the solid dispersions with porous structure Solid dispersion with a drug load of 30% w/w was a glass solution. Supercritical CO_2 did not affect the solid state of drug in the carrier. The solid dispersion was stable for 3 months at 40°C/75%RH	[74]
A model drug (blind name)	PVP K30	Sorbitol	First, the drug crystalline was converted to an amorphous state. Second, the obtained amorphous drug was incorporated in the carrier at 20% w/w drug load by hot melt extrusion process. The solid dispersion showed an increased bioavailability after oral administration as compared to the corresponding physical mixture	[78]

HPMC: Hydroxypropyl methylcellulose; HPβCD: Hydroxypropyl-β-cyclodextrin.

via the first procedure a tacrolimus–HPβCD complex could have been formed. The more rapid dissolution of the solid dispersion prepared via the first procedure compared to that prepared via the second procedure indicates that indeed the complex has been formed. The slowest dissolution rate as found for the solid dispersion prepared via the third procedure can be ascribed to the crystalline nature of the drug and the fact that the crystal size was not decreased.

Recently, nanosuspensions have been prepared by high pressure homogenization or wet ball milling. These nanosuspensions have been spray dried to render the formulation into a solid dosage form. In general, the nanosuspension consists of nano-sized drug crystals dispersed in an aqueous medium containing surfactants and/or polymers. The surfactants and/or polymers are needed to prevent aggregation of the drug particles and particle growth by Ostwald ripening. In addition, spray drying of nanosuspension requires excipients for forming hydrophilic matrices and aiding the spray-drying process. Thus, the obtained products can be regarded as solid dispersions. For example, a nanosuspension of the lipophilic drug candesartan cilexetil (10% w/v) in HPMC (2% w/v) and sodium dodecyl sulfate (1% w/v) was prepared after which mannitol (73% w/w with respect to the drug content) was added and then spray dried. Because of its low T_g (13°C), mannitol crystallized during spray drying and a fully crystalline solid dispersion was obtained. Furthermore, after reconstitution of the spray-dried powder with water, the particle size of drug was comparable to that of the

original nanosuspension. In addition, the dissolution rate of the solid dispersion was higher than that of drug microparticles and resulted in a higher bioavailability after oral administration in rats [90]. In another study, itraconazole nanosuspensions dispersed in aqueous solutions of different sugars, that is, sucrose, dextrose, lactose and mannitol, were spray dried. Spray-dried powder with mannitol as carrier yielded the optimal powder; it was free flowing and had low moisture content probably due to the crystalline nature of mannitol. In contrast, the spray-dried powder with lactose as carrier had high moisture content probably because lactose was amorphous; however, it was still free flowing. The spray-dried powders using sucrose or dextrose as carrier were sticky [91]. Most probably, these sugars were also amorphous and due to their high moisture content, their T_g was below ambient temperatures. Also, spray drying of nanosuspensions containing other lipophilic drugs such as fenofibrate [92], celecoxib [93] and cefpodoxime proxetil [94] using various carriers has been studied.

Colloidal silicon dioxide is often added to solutions or dispersions containing drug and carrier to be spray dried [95-98]. The reason is that this material has a very large specific surface area onto which the drug can deposit, by which it is very finely dispersed, resulting in excellent dissolution behavior. A concomitant advantage is that usually a high product yield is obtained and that the product shows improved flow properties.

A highly undesired phenomenon that may occur during spray drying is the formation of a sticky product at the outlet of the spray drier. Due to its stickiness, the product will adhere to the cyclone resulting in a low product yield. Several factors affect whether or not a sticky product is obtained. First, the glass transition temperature (T_g) of the carrier should be higher than the outlet temperature otherwise it will be in the rubbery and thus sticky state. For example, spray drying of carbamazepine with PVPVA 37 or PVPVA 64 has been investigated. These two polymers have different pyrrolidone:vinyl acetate monomer ratios yielding different T_g values. The T_g values of PVPVA 37 and PVPVA 64 are 55 and 106°C, respectively. The spray-dried product using PVPVA 64 was glassy whereas that using PVPVA 37 was rubbery. This result is caused by the fact of the outlet temperature of 74°C which is higher than the T_g of PVPVA 37 but lower than the T_g of PVPVA 64 [12]. Second, too high residual solvent content of the product can cause stickiness of product because solvents act as plasticizers reducing the T_g. The solvent can be removed more efficiently by increasing the inlet temperature and thereby accelerating the evaporation rate of the solvent and/or by using a taller drying chamber to allow enough time for solvent evaporation. Other solid dispersions [92-97,99-100] prepared by spray drying are summarized in **Table 3**.

3.2 Freeze drying

Another method to prepare solid dispersions is freeze drying. Freeze drying consists of three successive steps: freezing, primary drying and secondary drying. A sample to be freeze dried typically consists of a drug, excipients, and one or more solvents. During the freezing step, the solutes as well as the solvents are solidified by freezing. To explain what happens during this step, we consider a simplified system consisting of just one solute and one solvent (**Figure 2**). On cooling, initially only the solvent (e.g. water) crystallizes. Because the solvent crystallizes, the concentration solute in the remaining solution increases. This continues until the eutectic temperature (T_e) is reached, after which the solute also can crystallize by which a eutectic mixture is formed. However, the solute usually crystallizes slower than the solvent. Thus, if the solution is cooled sufficiently fast, the solute does not crystallize, but crystallization of the solvent continues until the glass transition temperature of the maximally freeze-concentrated fraction (T_g') is reached. If the solution is cooled further, the mobility of the molecules is strongly reduced. Due to the reduced mobility, neither the solute nor the solvent crystallizes further and a rigid glass is formed [101].

During primary drying, the solvent crystals are removed from the sample by sublimation. Thereto, the pressure in the freeze dryer is reduced. During primary drying, the product temperature should stay below the T_e (for eutectic mixtures) or T_g' (for glasses) to avoid solvent melting and thereby to avoid the sample to collapse. After sublimation of the solvent crystals, a porous cake is obtained.

During secondary drying, the unfrozen solvent is removed by desorption. Thereto, the shelf temperature is gradually raised, typically to ambient temperature, while the chamber pressure is further decreased. The unfrozen solvent is removed by diffusion through the freeze dried matrix and evaporation at the solid surface. Because amorphous products can absorb relatively large amounts of solvents, secondary drying is usually necessary to obtain a product with sufficiently low moisture content. In contrast, crystalline products usually adsorb only small amounts of solvent. Therefore, for crystalline materials, most of the solvents may already have been sublimated during primary drying, and secondary drying is not always necessary.

In the previous paragraphs, the sample composition was simplified to just one solute in a solvent to explain the freeze drying process. However, because the solubility of lipophilic compounds in water is low, usually these compounds are freeze dried from more complex co-solvent systems. Ideal co-solvents for freeze drying should have a high vapor pressure to ensure a high sublimation rate and a high melting point to allow the solvents to be frozen easily. An example of such a co-solvent is *t*-butyl alcohol (TBA). Its vapor pressure (41.25 mmHg) [102,103] and its melting point (T_m = 25°C) are relatively high [104]. More important than the melting temperature is the eutectic temperature of a co-solvent system. The water/TBA co-solvent system has relatively high eutectic temperatures of -5 and -3°C [103]. Therefore, it can be easily frozen at typical freeze drying temperatures. This in contrast to, for example, a water/ethanol co-solvent system, which

Table 3. Examples of solid dispersions prepared by spray drying.

Drug	Carrier	Solvent	Remarks	Ref.
Ibuprofen	Colloidal silicon dioxide:Tween® 80	Ethanol:water	Microsuspension was prepared prior to spray drying. The optimized concentration of colloidal silicon dioxide in the formulation was 1.5% w/w At a colloidal silicon dioxide concentration of 1.5%, the yield of microparticles was not affected by changing the Tween 80® concentration. In contrast, at a colloidal silicon dioxide concentration < 1.5%, the yields significantly decreased with increasing the Tween 80® concentration Dissolution of ibuprofen microparticles reached 100% in 3 min while that of unprocessed ibuprofen was < 10%	[95]
Cefpodoxime proxetil	Poloxamer 188: HPMC:glycerol	Water	Nanosuspension was prepared prior to spray drying After reconstitution of the spray-dried powder, the particle size was similar to that of the liquid nanosuspension (about 267 nm) The spray-dried powder showed a better dissolution behavior and bioavailability in rabbits than the marketed product	[94]
Glibenclamide	Gelucire® 50/13: colloidal silicon dioxide Gelucire® 44/14: colloidal silicon dioxide	Dichloromethane	Glibenclamide in these solid dispersions was amorphous Dissolution rate of a Gelucire® 44/14-based solid dispersion was slightly higher than that of a Gelucire® 50/14-based solid dispersion After storage for 3 months at 30°C/65%RH, the crystallinity of drug in these solid dispersions was slightly increased. However, the dissolution behavior of both solid dispersions was comparable to that of the corresponding freshly prepared solid dispersions	[97]
Simvastatin	PVP K30:colloidal silicon dioxide	Dichloromethane	Amorphous solid dispersion was obtained. The dissolution behavior was improved as compared with the corresponding physical mixture After storage for 3 months at 40°C/75%RH, the dissolution behavior of this solid dispersion was decreased, although the solid state of the drug in the solid dispersion remained amorphous	[96]
Fenofibrate	Lactose:sodium lauryl sulfate	Water	Nanosuspension was prepared prior to spray drying Fenofibrate in the spray-dried powder was predominantly amorphous Dissolution of the spray-dried powder yielded a supersaturated solution in the dissolution medium within 10 min after which recrystallization of the drug occurred Fenofibrate from the spray-dried powder dissolved faster than the marketed products	[92]
Celecoxib	Tween® 80 PVP K30:sodium lauryl sulfate	Ethyl acetate:water	Nanosuspension was prepared prior to spray drying During the spray-drying process, a sticky powder was found with the nanosuspension containing Tween® 80. In contrast, this problem was not observed with a spray-dried nanosuspension containing PVP K30 and sodium lauryl sulfate Dissolution behavior of spray-dried powder was significantly improved as compared to the unprocessed drug	[93]
Piroxicam	PVP K25	Ethanol:acetone	Amorphous solid dispersion was obtained The spray-dried powder showed that piroxicam interacted with PVP K25. The dissolution behavior was improved as compared to the corresponding physical mixture	[99]
Loperamide	PEG 6000	Dichloromethane	Dissolution of the spray-dried powder was faster than that of the corresponding physical mixture After the storage of the spray-dried powder for 1 month or 12 months at various conditions, the crystallinity of the drug increased in the order: 4°C/0% RH < 25°C/52% RH < 40°C/0% RH Dissolution rate of spray-dried powder stored at 25°C/52% RH and 40°C/0% RH was decreased as compared to the freshly prepared sample	[100]

HPMC: Hydroxypropyl methylcellulose.

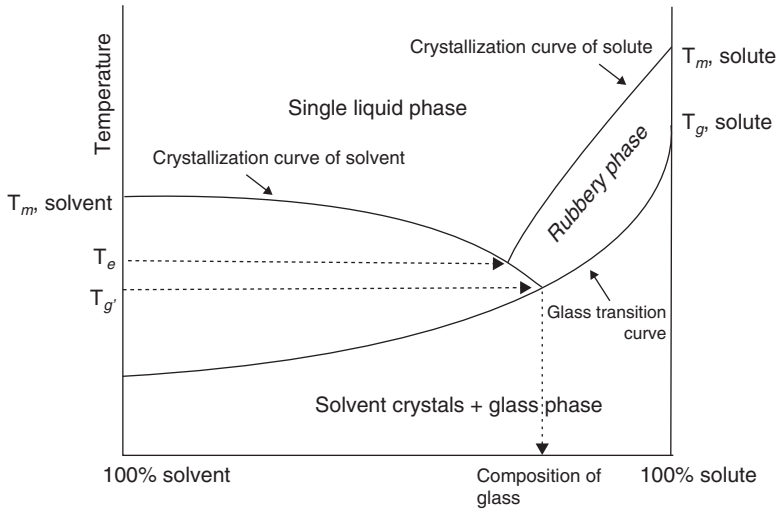

Figure 2. Phase diagram of a binary system during freezing.
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has a relatively low eutectic temperature of -124°C [105]. Another advantage of using TBA as a co-solvent is that small needle-shaped solvent crystals are formed on freezing. After sublimation of these needle-shaped crystals, a dry product layer with little resistance is formed which shortens the drying process [106]. Despite several limitations such as the limited level of residual solvents and the difficulty of handling or storage, co-solvent systems such as ethanol/water [107] and 1,4-dioxane/water [108] are used as well. Other practical aspects of freeze drying using co-solvent systems have been well reviewed by Teagarden and Baker [109].

High freezing rates can be achieved by using cryogenic liquids such as liquid nitrogen. Either vials containing the solution can be immersed in the cryogenic liquid or the solution is sprayed directly into the cryogenic liquid. By using a nozzle small droplets can be generated, which are then rapidly frozen. Thereafter, the frozen samples are transferred into a freeze dryer to continue with the primary and secondary drying stages. The nozzle position can be underneath [110,111] or above the surface of the cryogenic liquid [15]. The advantage of solid dispersions prepared by spray freezing into a cryogenic liquid is the formation of very small porous particles. Therefore, the surface area of these solid dispersions is significantly increased. For example, solid dispersions containing danazol and HPβCD prepared by spray freezing into liquid nitrogen had a surface area of 113.5 m^2/g, while the solid dispersion prepared without the spray freezing technique had a surface area of only 0.16 m^2/g. Consequently, the dissolution rate of the drug from the solid dispersion prepared by using spray freezing was faster than when the solid dispersion was prepared by freezing the bulk solution [110]. In addition, the type of solid dispersion that is formed can be influenced by the freezing method. For example, a water/TBA solution containing diazepam and inulin 4 kDa was frozen by two different methods: immersing a vial containing the solution in liquid nitrogen and spraying the solution into liquid nitrogen. A glass solution was obtained from spray freezing whereas a glass suspension was obtained when the vial was frozen in liquid nitrogen [15].

A freezing method that is suitable for large scale production is spraying the solution on the surface of a solid cold substrate. Purvis *et al.* sprayed a solution of the lipophilic drug repaglinide in a 1,4-dioxane/TBA/water co-solvent system on such a cold substrate. The frozen droplets were collected and then freeze dried. This resulted in amorphous dry particles that consisted of porous nanostructured aggregates. Dissolution of the drug from this amorphous solid dispersion was higher than that of the unprocessed drug [112]. Another technique that can be used for large scale production of solid dispersions is spray freeze drying by using a three-way nozzle [113]. Because a matrix/water solution and a drug/organic solvent solution flow separately through this nozzle, highly concentrated solutions can be spray freeze dried without the risk of unwanted recrystallization of any of the solutes from the solution before it is frozen. Therefore, relatively large amounts solid dispersion per batch can be produced.

Although the principle to obtain a solid dispersion is different, freeze drying can produce nanosuspensions, crystalline solid dispersions [114-116]. Van Eerdenbrugh *et al.* for example, freeze dried nanosuspensions containing nine different model drugs and D-α-tocopherol polyethylene glycol 1000 succinate as a stabilizer [114]. These solid dispersions showed the tendency to agglomerate, resulting in a lower dissolution rate. However, when excipients such as sucrose [115] or a surfactant [117] were added to the nanosuspension before drying, powder agglomeration could be prevented. Other solid dispersions [11,16,108,111,113,118-121] prepared by freeze drying or spray freeze drying are summarized in **Table 4**.

Table 4. Examples of solid dispersions prepared by freeze drying or spray freeze drying.

Drug	Carrier	Solvent	Remarks	Ref.
Curcumin (freeze drying)	HPMC-AS	1,4-Dioxane: water (90:10)	Amorphous solid dispersion (20% w/w drug load) was obtained Dissolution rate of the drug and oral bioavailability in rats from the solid dispersion were improved	[108]
Diazepam (freeze drying)	Inulin 1.8 kDa Inulin 4 kDa	*t*-Butyl alcohol: water (40:60)	Amorphous solid dispersion was obtained At 20% w/w drug load, the dissolution of inulin 4 kDa-based solid dispersion was faster than that of inulin 1.8 kDa-based solid dispersion	[121]
Diazepam (freeze drying)	Inulin 4 kDa PVP K30	*t*-Butyl alcohol: water (40:60)	Amorphous solid dispersion was obtained Rapid dissolution of the solid dispersions with a higher drug load (30% w/w) was achieved with PVP K30 due to the drug–carrier interaction. In contrast, diazepam did not interact with the inulin; therefore, the maximum drug load yielding fast dissolution was only 20% w/w	[11]
Fenofibrate (freeze drying)	Incorporation of sodium starch glycolate (superdisintegrant) in various carriers: inulin 4 kDa PVP K30 PEG 20000 HPβCD Mannitol	*t*-Butyl alcohol: water (40:60)	At about 50% w/w drug load, fenofibrate in all solid dispersions was predominantly crystalline state Dissolution rate of the solid dispersions increased in the order: mannitol < HPβCD < PVP K30 < PEG 20000 < inulin 4 kDa Dissolution behavior of inulin 4 kDa-based solid dispersion tablets was not changed after the storage for at least 3 months at 40°C/75% RH and 20°C/45% RH	[16]
Diazepam Fenofibrate Ritonavir Efavirenz (spray freeze drying)	Inulin 2.3 kDa PVP K30 Surface-active derivative of inulin	*t*-Butyl alcohol: water (60:40)	At 30% drug load, diazepam, ritonavir and efavirenz were fully amorphous in the carriers while fenofibrate was slightly crystalline in the carriers Overall, from the four drugs tested, the dissolution rate of the solid dispersions was increased in the order: inulin 2.3 kDa < PVP K30 < surface-active derivative of inulin Dissolution behavior of surface-active derivative of inulin-based solid dispersion tablets remained fast after the storage for at least 3 months at 40°C/75% RH and 20°C/45%RH	[118]
Tolbutamide (spray freeze drying)	HPMC 2910	1% Aqueous ammonia	A maximum drug load of 16.7% w/w in the carrier allowed the fully amorphous solid dispersion and the dissolution behavior was improved The specific surface area and the particle size of the solid dispersions were increased as the amount of HPMC increased in the solid dispersions	[120]
Flutamide (freeze drying)	β-CD HPβCD	*t*-Butyl alcohol: water (50:50)	At 16.7% w/w drug load, HPβCD allowed fully amorphous solid dispersion while β-CD did not HPβCD-based solid dispersion was more physically stable and dissolved faster than β-CD-based solid dispersion	[119]
Danazol (freeze drying and spray freeze drying)	Poloxamer 407	Mixtures of tetrahydrofuran and water	The crystallinity of the drug was found to be much lower after spray freeze drying than after freeze drying The specific surface area of the solid dispersion produced by spray freeze drying was substantially increased and the contact angle substantially decreased as compared to the solid dispersion produced by freeze drying The spray freeze-dried powder dissolved faster than the freeze-dried powder	[111]
Fenofibrate (freeze drying and spray freeze drying)	Mannitol	*t*-Butyl alcohol: water (40:60)	Fenofibrate in all solid dispersions prepared by freeze drying or spray freeze drying is highly crystalline Solid dispersions prepared by spray freeze drying dissolved faster than those prepared by freeze drying	[113]

HPMC: Hydroxypropyl methylcellulose; HPβCD: Hydroxypropyl-β-cyclodextrin.

3.3 Supercritical fluid precipitation

Another method to prepare solid dispersions of poorly water-soluble drugs is supercritical fluid precipitation. A supercritical fluid is a fluid that is pressurized above its critical pressure (P_c) and heated above its critical temperature (T_c). A supercritical fluid exists as a single fluid phase with physicochemical behavior in between a liquid and a gas. The liquid-like characteristics are beneficial for dissolving the solute while the gas-like characteristics are advantageous for rapid precipitation of solutes. CO_2 is commonly used for supercritical fluid precipitation because it is non-toxic, non-flammable, cheap, recyclable after processing and environmentally friendly. Furthermore, due to the relatively low critical point of CO_2 (74 bar and 31°C), it allows for easy processing, which makes it suitable for pharmaceutical products [122].

Supercritical fluid precipitation can be separated into two categories: first, the supercritical fluid can be used as a solvent and second, the supercritical fluid can be used as an antisolvent [123]. When the supercritical fluid is used as solvent, the drug is dissolved in the supercritical fluid and subsequently this supercritical solution is sprayed through a nozzle into an expansion chamber in which the pressure and/or the temperature are decreased. Due to the decreased pressure and/or temperature, the solubility of drug in supercritical fluid decreases, leading to precipitation of the drug. This process is known as rapid expansion of supercritical solutions (RESS). Krukonis was the first who applied the RESS technique to produce fine particles with a narrow size distribution [124]. Initially, this method was used for precipitating pure drugs [125,126]. However, supercritical CO_2 has also been used to prepare solid dispersion, for example, a solid dispersion of piroxicam incorporated in β-CD [127]. The main disadvantage of using supercritical CO_2 as a solvent to prepare solid dispersions is that both the drug and the hydrophilic carrier have to be soluble in supercritical CO_2 which is for many drug–carrier combinations not the case.

When the supercritical fluid is used as an antisolvent, first a solution of the drug and a carrier is prepared. This solution is then saturated with supercritical CO_2, resulting in a decreased solubility of the drug and the carrier in the organic solvent and consequently in precipitation of the drug and the carrier. Two requisites of this method are: i) the drug and carrier should be soluble in the organic solvent but not soluble in the mixture of supercritical CO_2-organic solvent and ii) the organic solvent should be miscible with supercritical CO_2. The supercritical fluid as antisolvent was first applied by Gallagher *et al.* [128]. Using supercritical fluid as an antisolvent, different ways to introduce a solution of sample and supercritical CO_2 into a precipitating chamber which have been used are gas antisolvent precipitation, precipitates by compressed antisolvent, supercritical antisolvent, aerosol solvent extraction system and solution enhanced dispersion by supercritical fluids [129].

The effects of drug load and the concentration of drug and carrier in the solution on the solid state were studied by Kluge *et al.* Phenytoin was incorporated in PVP K30 at different drug loads. The drug in solid dispersion with drug loads below 40% w/w was amorphous, whereas at a drug load higher than 40% w/w the drug was partially amorphous and partially crystalline. Furthermore, it was found that a change in total concentrations of phenytoin and PVP K30 in the starting solution did not affect the crystallinity of the drug in carrier [130].

Other factors such as the type of carrier and type of organic solvent can influence the characteristics of solid dispersions and the product yield. For example, oxeglitazar at a drug load of 50% w/w was incorporated in different carriers: PEG 8000, poloxamer 407 and PVP K17. Solid dispersions with PEG 8000 and poloxamer 407 yielded needle-like drug crystals partially covered with the carriers. Solid dispersion with PVP K17, on the other hand, resulted in irregular shaped particles with a lower degree of crystallinity. Furthermore, a higher amount of residual solvent was found with PVP K17 as a carrier than when other carriers were used. In the same study, different organic solvents (ethanol, dichloromethane and chloroform) were evaluated. When dichloromethane and chloroform were used, a higher product yield was obtained than when ethanol was used. Nevertheless, the use of chloroform resulted in the lower amount of drug which can be incorporated in the carriers as compared to the theoretical value. Overall, PEG 8000 and poloxamer 407 as carriers and dichloromethane as a solvent resulted in the highest product yield, lowest residual solvent content and highest efficiency of drug incorporation. However, poloxamer 407 yielded the higher polymorphic purity of drug in the carrier than PEG 8000. Therefore, the optimum carrier and solvent for this study were poloxamer 407 and dichloromethane, respectively. In addition, these solid dispersions showed improved dissolution behavior of oxeglitazar than when a physical mixture was used [131]. Other solid dispersions [99,132-142] prepared by using supercritical fluid as an antisolvent are summarized in **Table 5**.

4. Expert opinion

The application of solid dispersions has successfully improved the bioavailability of lipophilic drugs. In this review, the most commonly applied methods to prepare solid dispersions and formulation considerations are described. The advantages and disadvantages of the described methods are summarized in **Table 6**. In addition, a decision tree to help the selection of described methods is shown in **Figure 3**. Many studies have proven that solid dispersions prepared by these methods can increase the dissolution rate of several lipophilic drugs and thereby their bioavailability. Other critical aspects related to solid dispersions are that they should be stable on storage and that they can be produced at a large scale. Marketed products which have been produced by solid dispersion technology have been reported previously by Janssens and Van den Mooter [143].

Table 5. Examples of solid dispersions prepared by supercritical CO_2 as antisolvent.

Drug	Carrier	Solvent	Remarks	Ref.
Nifedipine	PEG 4000	–	Supercritical CO_2 was dissolved in melts of drug–PEG instead of using a solvent. Drug dissolution improved. Drug load not described	[142]
Carbamazepine	PEG 4000	Acetone	Drug was crystalline (8.3% w/w drug load). Drug dissolution was improved	[141]
Carbamazepine	PEG 8000 PEG 8000:Gelucire® 44/14 PEG 8000:TPGS	Methanol	Drug was crystalline in all solid dispersions (16.7% w/w drug load) Dissolution rate was increased in the order: PEG < PEG + Gelucire® < PEG + TPGS	[140]
Carbamazepine	PVP K30 PVP K30:Gelucire® 44/14 PVP K30:TPGS	Methanol	Drug was amorphous in all solid dispersions (16.7% w/w drug load) Intrinsic dissolution rate was increased in the order: PVP + Gelucire® < PVP + TPGS < PVP	[138]
Piroxicam	PVP K25	Dichloromethane	Fully amorphous solid dispersion (20% w/w drug load) was obtained. Dissolution of drug was improved	[99]
Indomethacin	PVP K90	Dichloromethane: acetone (20:80)	Fully amorphous solid dispersions were obtained with drug loads up to 50% w/w The solid dispersion (50% w/w drug load) remained stable for 7 months at 75% RH and room temperature	[132]
Itraconazole	Hydroxypropyl-β-cyclodextrin	Dichloromethane: ethanol (30:70)	Complexes with a maximum molar ratio of 1:2 (drug:carrier) were formed. The dissolution rate of the drug was improved	[134]
Itraconazole	HPMC 2910	Dichloromethane: ethanol (60:40)	The drug was amorphous in the solid dispersion (60% w/w drug load) The pharmacokinetics of the drug from the solid dispersion in rats was similar as the marketed product	[137]
Felodipine	HPMC 2910 HPMC 2910:HCO-60 HPMC 2910:HCO-60: poloxamer 188 HPMC 2910: HCO-60: poloxamer 407	Dichloromethane: ethanol (45:55)	The drug was amorphous in all solid dispersions (about 10% w/w drug load) The dissolution rate of the drug from the solid dispersions was increased in the order: HPMC < HPMC 2910:HCO-60: poloxamer 188 < HPMC 2910:HCO-60 < HPMC 2910:HCO-60: poloxamer 407	[135]
Cilostazol	Poloxamer TPGS Gelucire®	Dichloromethane	Surfactants (1%) were added to the drug solution. The particle size of the drug was decreased in the order: Gelucire® > drug without surfactant > TPGS > poloxamer	[133]
Cefuroxime axetil	PVP K30 HPMC 2910	Dichloromethane: ethanol (60:40)	Solid dispersions (40% w/w drug load) prepared from PVP and HPMC were fully amorphous Dissolution rate of drug was increased for both carriers	[136]
A model drug (blind name)	Mannitol Eudragit® E100	Dimethyl sulfoxide: methanol (20:80) for mannitol Dimethyl sulfoxide: acetone (30:70) for Eudragit® E100	Using Eudragit® E100 yielded fully amorphous solid dispersion (20% w/w) whereas using mannitol did not	[139]

HCO-60: Polyoxyethylene (60) hydrogenated castor oil; HPMC: Hydroxypropyl methylcellulose; PVP: Polyvinylpyrrolidone; TPGS: D-α-tocopherol polyethylene glycol 1000 succinate.

The fusion method is the easiest method to prepare solid dispersions. Because it is a fast process, this method is useful to screen formulations. However, due to the difficulty of controlling the temperature during preparation, phase separation between drug and carrier can easily occur. Because this phase separation cannot be controlled well, it may result in the formation of large drug particles which obviously will dissolve slowly. In addition, when amorphous drug particles are formed, undesired crystallization during storage can occur. Therefore, due to the poor temperature control, the fusion method is considered less suitable for large scale production.

Table 6. Advantages and disadvantages of fusion, hot melt extrusion, spray drying, freeze drying and supercritical fluid drying.

Method	Advantages	Disadvantages
Fusion	Short time process Solvent-free	Not suitable for thermally labile drugs
Hot melt extrusion	Solvent-free Good controlled temperature system Large scale production available	Not suitable for thermally labile drugs Carriers without proper thermoplastic properties cannot be used
Spray drying	Short time process Micro- to nano-particulates obtained Robust process Large scale production available	Possible solvent residue in the product
Freeze drying	Robust process Large scale production available Mild production condition	Possible solvent residue in the product Time consuming High cost
Supercritical fluid drying (as antisolvent)	Mild production condition	Possible solvent residue in the product Solubilizing power of supercritical fluid (CO_2) limited

Hot melt extrusion is a similar method as the fusion method because in both methods the drug and carrier are first heated and subsequently cooled to obtain the solid dispersion. However, hot melt extrusion is more robust than the fusion method as it is a method by which the drug can be well mixed with the carrier at a controlled temperature leading to a homogeneous and, therefore, stable and reproducible product. Recently, a solid dispersion was successfully prepared at large scale by hot melt extrusion. This indicates that hot melt extrusion is a viable method and potentially more products prepared by this technique can reach the pharmaceutical market. This explains a recent trend in literature that describes methods to investigate the choice of carriers for specific drugs. Several synthetic polymeric carriers are available for this method. The main disadvantage of hot melt extrusion is that it is limited to thermally stable drugs and carriers with thermoplastic properties.

Spray drying and freeze drying are methods to produce solid dispersions that have been used for many years. The influence of process parameters on the product properties has been extensively studied. Spray drying can be performed as a continuous process and is, therefore, suitable for large scale production. Freeze drying is a batch process but can also be used for large scale production although it is expensive and time consuming. Therefore, the research trends that can be found in recent literature are process modifications to increase the versatility of these methods, for example, spray drying at low temperature that can be applied to carriers with a low melting point or glass transition temperature. Another example is the adjustment of the freeze drying process into a spray freeze drying process. The main advantage of this adjustment is that the freezing rate is high and can be controlled well. Another interesting development is spray drying or freeze drying of nanosuspensions of drugs. It is well known that nanosuspensions often have an improved bioavailability compared to larger drug forms. Nevertheless, it is a liquid and often not stable dosage form. In general, solid and more stable dosage forms are preferred; therefore, the transformation of nanosuspensions into a dry powder form seems interesting. A dry powder can be filled into capsules or processed into tablets. Although, spray drying and freeze drying are promising methods to prepare solid dispersion, the presence of residual (toxic) solvents in the final product remains a concern as are different aspects of scale up of these processes.

The most recently used method to prepare solid dispersions is supercritical fluid precipitation. So far, supercritical CO_2 is the most commonly used supercritical fluid in processes where the supercritical fluid acts as an antisolvent. Because this process requires that the supercritical fluid and the organic solvents are miscible, the number of suitable solvents is limited. Most studies have used ethanol and/or dichloromethane. Fortunately, many different types of carriers can be used with this process. Many studies have shown promising results. However, extensive investigation of process parameters is required, because these parameters usually determine the properties of the solid dispersions and the product yield. Because large scale production of pure drugs by this method has successfully been performed, we do not expect major technical difficulties with large scale production of solid dispersions by this method.

An important issue is the physical stability of solid dispersions. In general, the solid state of the drug incorporated in carriers can be amorphous, crystalline or a combination of both. Amorphous solid dispersions are thermodynamically less stable than crystalline solid dispersions. Although many studies have shown that amorphous solid dispersions prepared by the described methods are stable in short-term stability studies, long-term stability is still challenging. Therefore, the interest in the preparation of crystalline solid dispersions is growing. Furthermore, a better understanding of the effects of process conditions and type of drug and carrier on the

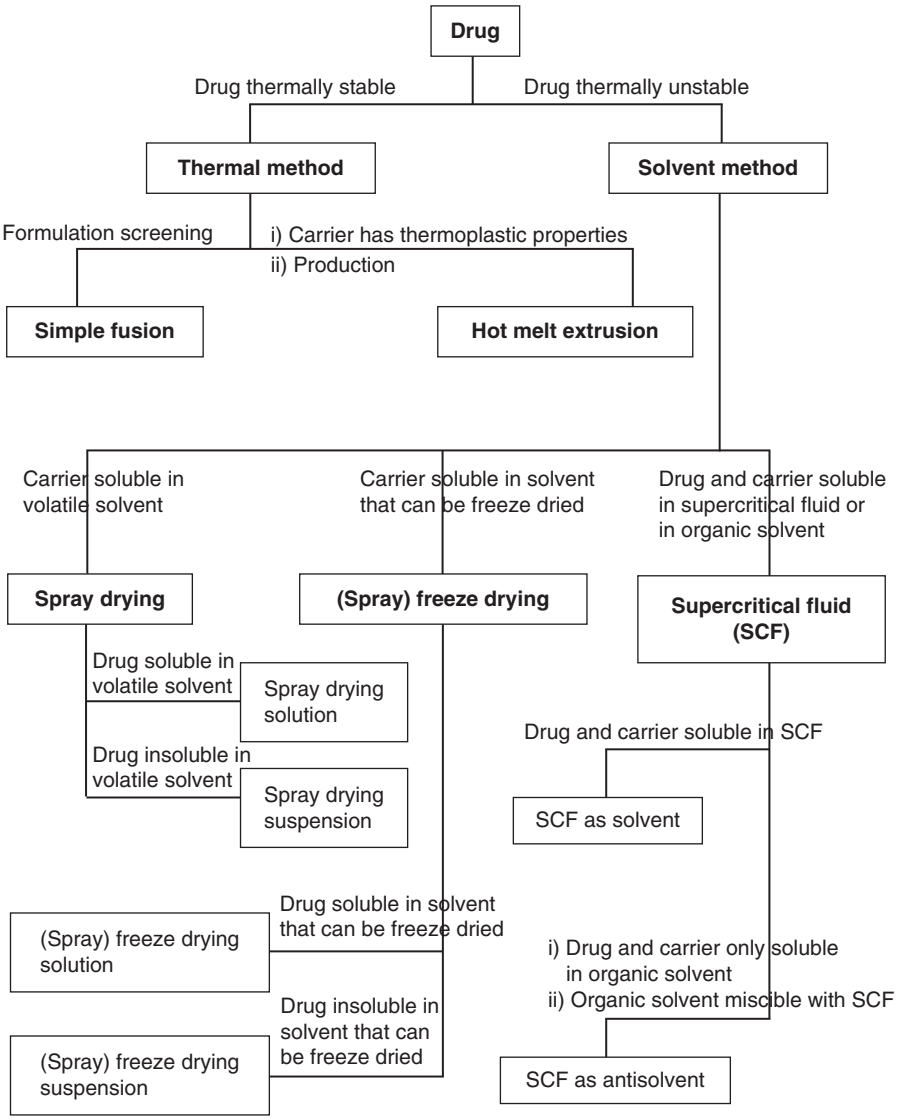

Figure 3. A decision tree for the selection of the production process of solid dispersions.

properties of the final product is required. This will be facilitated by the growing number of in-line analytical instruments that are available to investigate phenomena occurring during the production processes.

Declaration of interest

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

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