Expert Opinion

Solid dispersions, Part I: recent evolutions and future opportunities in manufacturing methods for dissolution rate enhancement of poorly water-soluble drugs

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Introduction: In recent years, the number of active pharmaceutical ingredients with high therapeutic impact, but very low water solubility, has increased significantly. Thus, a great challenge for pharmaceutical technology is to create new formulations and efficient drug-delivery systems to overcome these dissolution problems.
Areas covered: Drug formulation in solid dispersions (SDs) is one of the most commonly used techniques for the dissolution rate enhancement of poorly water-soluble drugs. Generally, SDs can be defined as a dispersion of active ingredients in molecular, amorphous and/or microcrystalline forms into an inert carrier. This review covers literature which states that the dissolution enhancement of SDs is based on the fact that drugs in the nanoscale range, or in amorphous phase, dissolve faster and to a greater extent than micronized drug particles. This is in accordance to the Noyes–Whitney equation, while the wetting properties of the used polymer may also play an important role.
Expert opinion: The main factors why SD-based pharmaceutical products on the market are steadily increasing over the last few years are: the recent progress in various methods used for the preparation of SDs, the effect of evolved interactions in physical state of the drug and formulation stability during storage, the characterization of the physical state of the drug and the mechanism of dissolution rate enhancement.

Keywords: cyclodextrins complexation, kneading, poorly water-soluble drugs, solid dispersions, solubility enhancement, solvent evaporation, spray drying, wet milling

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1. Introduction

According to the Biopharmaceutics Classification System (BCS), drug compounds are divided into four classes taking into account the drug aqueous solubility and drug intestinal permeability, in order to outline the importance of the aqueous solubility and dissolution behavior of drugs for their bioavailability, that is, their therapeutic efficacy and safety [1]. Class I drugs have high bioavailability and provide no challenge. Class IV drugs are pharmaceutical bricks which will never make it to the market. Class II and Class III drugs have a poor bioavailability because of their low solubility and their low membrane permeability, respectively. Drug candidates with successfully improved bioavailability by a solubilization technique belong to Class

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Article highlights.

- 'Solid dispersion' (SD) is one of the earlier, yet still favorable, approaches for overcoming drug dissolution and increasing solubility of poorly water-soluble drugs.
- The numbers of pharmaceutical products on the market based on SDs are steadily increasing in recent years.
- Significant progress has been achieved in recent years on optimizing the used methods in the manufacture of SDs and the application of new and innovative materials that maximize the benefits of SDs.
- Solvent evaporation, wet-milling process, spray drying and drug complexation with cyclodextrins are some of the most commonly used techniques.

This box summarizes key points contained in the article.

II, which means that their bioavailability is only limited by their poor aqueous solubility.

Poorly water-soluble drugs show a number of negative clinical effects, such as high local drug concentrations at the sites of the aggregate deposition, which could be associated with local toxic effects of the drug and decreased systemic bioavailability [2]. These drugs tend to be eliminated from the gastrointestinal tract before they get the opportunity to fully dissolve and be absorbed into the blood circulation. It is estimated that 25 – 40% of the already known, as well as about the same percentage of newly developed drug substances, exhibit poor solubility characteristics and thus present a problem in pharmaceutical formulations.

The modified Noyes–Whitney equation provides some hints regarding how the dissolution rate of very poorly soluble compounds can be improved to minimize the limitations to oral bioavailability [3,4]:

$$dC/dt = AD(Cs - C)/h$$

where dC/dt is the rate of dissolution, A is the surface are available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. According to this equation, the dissolution rate of a drug is proportional mainly to its effective surface area which can be increased by: decreasing the particle size of the drug to submicron range, optimizing the wetting characteristics of the compound surface, decreasing the diffusion layer thickness, ensuring sink condition for dissolution and improving apparent solubility of the drug under physiologically relevant conditions.

The concept of solid dispersions (SDs) is one formulation strategy utilized to improve bioavailability of poorly soluble compounds [5,6]. The properties and performance of SDs have, therefore, been explored now for some decades, in which the drug is dispersed mainly in nanocrystals or in amorphous state. SDs may be defined as pharmaceutical forms in which the drug is dispersed in a biologically inert matrix, usually in order to enhance the drug's oral bioavailability through improvement of its dissolution rate in aqueous media [7]. Effective techniques for drug nanocrystal production in SDs are usually precipitation-based processes, such as spray drying and supercritical antisolvent process, spray freeze drying into liquid, evaporative precipitation into aqueous solution and liquid solvent change process [8-10]. Furthermore, except nanocrystal formation, one of the underlying principles of SDs is the drug suspension in amorphous state, which is considered to be more soluble than the crystalline state. Amorphous drugs can have as much as 10- to 1600-fold higher solubility than their crystalline forms [11,12]. Typical mechanisms for the improvement of dissolution characteristics of drugs by the amorphous SD approach are the reduction of particle size, absence of crystallinity and improved wettability [13-18].

Researches on new SDs and the related fabrication processes have been widely reported in literature during the past several decades [19-21], and today a lot of SD products are marketed: Kaletra® (Abbott), Intelence® (Tibotec), Certican® (Novartis), Isoptin SR-E® (Abbott), Nivadil® and Prograf® (Fujisawa Pharmaceutical Co., Astellas Pharma, Inc.), Rezulin® (Sankyo), Sporanox® (Janssen Pharmaceutic), Sirolimus®, which is marketed by Wyeth as Rapamune®, Tricor® (Abbott), Megace® ES (Par Pharmaceutical), Emend® (Merck) [7], and Toramat®, Vociflon® (**Figure 1**), Montelukast®, Palibone®, Iasibon®, Razilan® and Ostiral® all from Pharmathen S.A.

The preparation of SDs is a dynamic process and new strategies, materials and techniques are developed continuously. The present review focuses on recent advantages of SDs, mainly in manufacturing methods, and their future opportunities for dissolution enhancement of poorly water-soluble drugs.

2. SD manufacturing methods

2.1 Solvent evaporation

The most common method used for dissolution enhancement of class II drugs is solvent evaporation. According to this method, the drug and the chosen polymers (carriers) are dissolved in a common organic solvent at different weight ratios. The solvent(s) is then removed at room or elevated temperatures (40 – 60°C) under stirring conditions and the resultant SDs are collected. According to this procedure, the drug can be dispersed in crystalline or amorphous state, while the physical state of the drug is mainly affected by the used carrier, the drug amount and the interactions between drug and carrier. The advantage of this method is that in most cases the drug is finely mixed with the carrier and molecular level dispersions of the drug can be achieved. The main drawbacks are: the use of organic solvents with issues of toxicity, safety hazards and solvent residuals; the possible precipitation of the drug into various polymorphic forms, which have different solubilities and bioavailabilities; and the low physical stability of the drug in the final dispersion.

Using solvent evaporation, polyvinylpyrrolidone (PVP) and PEG SDs with felodipine or hesperetin having up to 20 wt%

Figure 1. Pharmaceutical products prepared using SD methods from Pharmathen S.A.
SD: Solid dispersion.

drug were prepared with ethanol as the common solvent [22]. PVP formulations with low drug load proved to be amorphous, as no crystalline felodipine or hesperetin drugs were detected using differential scanning calorimetry (DSC) and WAXD. However, in the case of PEG SDs the drugs were in the crystalline phase. It seems that during crystallization of PEG matrix, the drug, which was in amorphous state, can crystallize also [23]. The formed interactions can also play a significant role in the drug physical state and this can affect the dissolution rates of the prepared SDs [24]. The solubility enhancement of crystalline SDs (CSDs) was lower than when amorphous PVP was used as a drug carrier [25]. The rate of dissolution enhancement was also dependent on the type of solvent used in the preparation of SD formulations. In a recent study, different solvents (ethanol, acetone and water) were used as a second variable in the preparation of glucosamine HCl SDs with carbamazepine (CBZ) poorly water-soluble drug [26]. It was found that the dissolution efficiency was ranged as follows: ethanol > acetone > ethanol–water > acetone–water when the ratios of drug:carrier were 4:1 and 2:1. The presence of water in the preparation of CBZ–glucosamine SDs reduced the dissolution rate of CBZ, which was attributed to the formation of dihydrate form. It was also shown that morphology of particles and concentration of glucosamine played an important role in the dissolution rate of CBZ from SDs. However, the effect of these parameters was overshadowed by the type of CBZ polymorph.

The carrier amount, which in some cases also plays the role of emulsifier, is very important in SDs prepared by solvent evaporation. When hydrophilic carriers were used, such as PEG 6000, it was found that the solubility of gliclazide increased with increasing amount of PEG 6000 in water [27]. Gibbs free energy (Gotr) values were all negative, indicating the spontaneous nature of gliclazide solubilization, and they decreased with increase in PEG 6000 concentration, demonstrating that the reaction conditions became more favorable as the concentration of PEG 6000 increased. DSC and X-ray diffraction (XRD) studies indicated the microcrystalline or amorphous state of gliclazide in SDs of gliclazide with PEG 6000, which is very common in SDs prepared by solvent evaporation.

The main goal of SDs prepared by solvent evaporation is the formation of amorphous drug dispersions. In such a case, it was believed that the drug is dispersed in molecular distribution. However, this view has slightly changed in recent years, taking into account new findings. It was found that the drug can also exist in the form of nanodispersions, as in the case of PVP–naringenin–hesperetin SDs, which were prepared using ethanol as solvent for both polymer and drugs [28]. It was found that naringenin and hesperetin drugs were dispersed not only in a molecular level, but also in the form of amorphous nanoparticles and their dissolution rate was dramatically increased in the PVP–naringenin–hesperetin (80/20, w/w) systems due to the amorphization of the drugs. At a concentration higher than 20 wt%, the drugs crystallized and the dissolution rate was reduced. Thus, drug:polymer ratios in SDs have an impact on the drug's physical state, average particle size, morphology and dissolution profile [29,30]. From a similar study, it was found that SDs containing up to 50 wt% felodipine were completely amorphous and with a combination of scanning electron microscopy (SEM), transmission electron microscopy (TEM) micrographs and micro-Raman mapping it was revealed that felodipine was also dispersed in the form of nanoparticles in the PVP matrix (**Figure 2**). Due to the high spatial resolution of TEM, it was established that these nanoparticles were not uniform particles, but rather agglomerates of individual particles with sizes smaller than 5 – 10 nm. Moreover, micro-Raman mapping allowed us to observe the size and spatial distribution of domains where the drug existed as molecular or nanodispersions. Experimental evidence presented in this work contradicts the common belief that amorphous poorly water-soluble drugs exist only in the state of molecular dispersion inside a polymer matrix by demonstrating that both types of dispersions (molecular level and nanodispersions) can coexist.

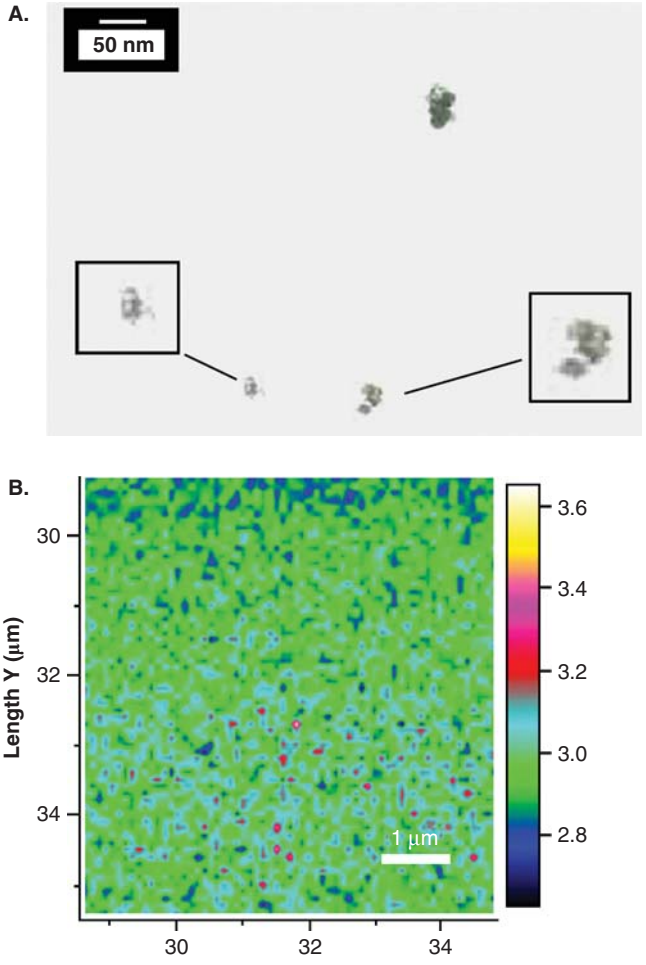

Figure 2. A) Transmission electron photomicrographs of PVP–Felodipine 90/10 w/w solid dispersion and **B)** XY micro-Raman mapping of PVP–Felodipine 90/10 w/w solid dispersion (red color indicates higher concentrations of felodipine drug).
PVP: Polyvinylpyrrolidone.

The same was also found in PVP–nimodipine SDs [31]. DSC and modulated-temperature DSC in combination with X-ray powder diffractometry (XRPD) and SEM studies showed that nimodipine was amorphous in SDs of 10 or 20 mass%, and mainly dispersed on a molecular level and less in nanodispersions. This behavior was attributed to the hydrogen boding interactions taking place between the amine group of nimodipine and carbonyl group of PVP. However, at higher drug loadings, crystal reflections in XRPD patterns and melting peaks of nimodipine in DSC traces indicated the presence of drug in crystalline form. Micro-Raman studies in combination with SEM micrographs showed that the mean particle size increased with drug content in the formulations up to 10 µm. Moreover, both XRPD patterns and micro-Raman spectra seemed to indicate that nimodipine crystallized in a second, thermodynamically stable, crystal modification II. The physicochemical characteristics of nimodipine and the particle size distribution directly affected the dissolution rate enhancement, which was higher in amorphous dispersions.

Except single solvents, as was reported previously, combination of co-solvents for the preparation of SDs can also be used [32]. The solubilizing power of the PVPK30–thiabendazole SDs was higher at lower temperatures and it decreased nonlinearly as the concentration of ethanol in water increased. The SDs produced the highest solubility increase in pure water (750%). In the case of the non-aqueous mixture, the solubility increase by SDs was smaller (20 – 30%). Similar findings were also reported in the case of simvastatin (SIM) and hydroxypropylmethyl cellulose (HPMC) K3LV SDs using the co-solvent evaporation method [33]. Results of this study show the conversion of the crystalline form of SIM into amorphous form and the dissolution rate remarkably increased in the co-solvent-evaporated mixtures compared to SIM. Co-solvent procedure was also used in a recent study [34]. Three SDs containing poorly water-soluble tacrolimus were prepared with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and dioctyl sulfosuccinate (DOSS) using the solvent-evaporation method with a methylene chloride–ethanol mixture, the solvent-wetting method with ethanol and the surface-attached method with water, respectively [34]. The solubility and dissolution of the drug were significantly improved in the order of the tacrolimus-loaded SD prepared by: solvent-evaporation method > solvent-wetting method > surface-attached method. The SDs prepared by solvent evaporation appeared as an aggregated form consisting of smaller amorphous nanoparticles. In particular, the SD prepared by the solvent-evaporation method improved solubility by about 900-fold and dissolution of tacrolimus by 15-fold because of its reduced particle size, increased surface area and close contact between the hydrophilic carrier and the drug. In the solvent-wetting method, the drug, which was changed to an amorphous form, was attached onto the surface of undissolved carriers. However, the SD prepared by the surface-attached method gave an unchanged crystalline form. In this SD, the carriers were attached to the surface of the undissolved drug, resulting in changing the drug from being hydrophobic to hydrophilic. As the crystal form of drug in this SD was not converted to the amorphous form, unlike other SDs, it gave relatively less solubility and dissolution of the drug than did the others.

Instead of polymers, inorganic nanoparticles have also been used extensively in recent years as drug carriers, and for dissolution rate enhancement of poorly water-soluble drugs, and such formulations can be prepared mainly by solvent evaporation technique. Impregnation of porous SiO_2 (Sylysia) with carvedilol from acetone solution was used to improve dissolution of this poorly water-soluble drug [35]. The impregnation procedures resulted in a significant improvement of drug release compared to dissolution of pure carvedilol or its physical mixtures with Sylysia. The results showed that when the drug precipitated in a thin layer within the carrier the dispersion retained a high specific surface area, micro-pore volume and

drug-release rate from the SD. Increasing the amount of drug in the SD caused particle precipitation within the pores that decreased the carrier's specific surface area and pore volume and decreased the release rate of the drug. The results also suggested that the amorphous form of carvedilol, the improved wettability and weak interactions between the drug and carrier in the SD also contributed to improved dissolution of the drug from the dispersion.

Surface functionalized mesoporous silicon (pSi) microparticles were also reported as an SD carrier for improving dissolution and enhancing the orally administered pharmacokinetics (fasted rat model) of indomethacin (IMC), which is used as a model poorly soluble BCS type II drug [36]. IMC was loaded via immersion/solvent evaporation onto the thermally oxidized pSi particles, which provided a stable hydrophilic matrix with a nanoporous structure. IMC molecules were encapsulated in a noncrystalline state due to geometric confinement in the nanopores; stability of the noncrystalline state was demonstrated for several months under accelerated storage conditions. The pSi carrier facilitated accelerated immediate release of IMC and enhanced oral delivery performance in comparison with crystalline IMC and indocid, that is, a four times reduction on t_{max}, a 200% increase on C_{max} and a significant increase in bioavailability. In the above SDs, the drug was dispersed in an extremely high surface area 100 – 1000 m^2/g that these inorganic particles have. This results in the drugs being dispersed in an amorphous form or in nanocrystals level. All these contributed to the substantial enhancement of the drug dissolution rate.

High surface areas for drug dispersion can be also prepared in foamed polymers. Such spherical mesocellular foam (MCF) with a continuous 3D pore system was synthesized using Pluronic 123 triblock polymer as a surfactant coupled with cetyltrimethyl ammonium bromide as a co-surfactant (**Figure 3**) [37]. A model drug, telmisartan (TEL), was loaded onto MCF via a procedure involving a combination of adsorption equilibrium and solvent evaporation. The drug-release rate and the drug loading efficiency of spherical MCF were compared with those of fibrous MCF SBA-15. Investigations using nitrogen adsorption, SEM, TEM, wide-angle X-ray scattering, DSC and HPLC demonstrated the successful incorporation of TEL into the MCF host. It was found that spherical MCF had a high drug loading efficiency up to 42.9% (drug weight/total weight) and higher than that of SBA-15 with a pore diameter of 6.5 nm. As can be seen from **Figure 3A**, substantial dissolution enhancement of TEL was achieved compared with crystalline TEL and TEL–SBA-151 formulation.

Compared with other methods, solvent evaporation method was reported to be more appropriate for the preparation of SDs, based on the dissolution rate results [38]. Ritonavir SDs were prepared by solvent evaporation and melt mixing in order to investigate them for *in vitro* and *in vivo* performance for enhancing dissolution and bioavailability, respectively. The SD was prepared using gelucire as a carrier in a 1:4 ratio. *In vitro* dissolution studies were performed in 0.1 N HCl and biorelevant media showed enhanced dissolution rate as compared to pure drug. It was also observed that the release profile of SD was dependent on the method of preparation. The SD prepared with the melt method for gelucire showed less release (80.9%).

As a further addition to the common solvent evaporation method, in recent years a novel solid-dispersion system termed 'surface-attached SD' has been developed [39]. In this case, the drug is dissolved and dispersed in the surface of drug carriers after water removal as monolayer. Unlike other SDs, surface-attached SD was prepared with water and carriers without an organic solvent for enhancing the solubility and stability of poorly water-soluble drugs. This solid-dispersion method has several advantages over other methods on an industrial scale, such as there being no necessity to remove an organic solvent, less potential toxicity and no danger of explosion of organic solvents. Furthermore, this SD could enhance the solubility and bioavailability of poorly water-soluble drugs without changing their crystalline state.

2.2 Kneading

Kneading is maybe the simplest technique to prepare drug SDs. According to this procedure, the drug and the appropriate polymers, as physical mixtures in different ratios, are triturated using a small volume of ethanol–water (1:1) solution to give a thick paste. Drug or some of the used polymers should be soluble in water or mainly in ethanol. The prepared paste is kneaded for different times, 10, 20 or 30 min, for the drug to be dissolved and dispersed in the used carrier and then dried at medium temperature (40 – 60°C) in an oven. The dried mass is pulverized, passed through the appropriate mesh sieve size and used for the preparation of the final formulation. In this case, the drug is dispersed in the carrier as microcrystals or in amorphous state, increasing its dissolution rate. The rationale behind the selected kneading method is that it is economic, environmentally friendly and avoids thermal degradation of drug, usage of organic solvent and sophisticated and more expensive equipments. Also, SD powders which are obtained by this method and selected polymers are physico-chemically stable and can be easily formulated in a tablet dosage form by direct compression method.

The kneading technique was used to prepare SDs of meloxicam (MLX), a practically water-insoluble drug, using a hydrophilic polymer, poloxamer 188 (PXM) [40]. The use of a factorial design approach helped in optimization of the preparation and formulation of SD. Fourier transform infrared (FTIR) spectroscopy, DSC, XRD studies and SEM demonstrated that enhanced dissolution of MLX from the SD might be due to a decrease of the crystallinity of MLX and PXM. Similar tablets were also prepared from SD of furosemide in sodium starch glycolate (SSG) at ratios of 1:1 and 1:2 (furosemide):(SSG) using the kneading method [41]. XRD, DSC, FTIR spectroscopy and dissolution studies indicated that the SD formulated at a 1:2 ratio showed a 5.4-fold increase

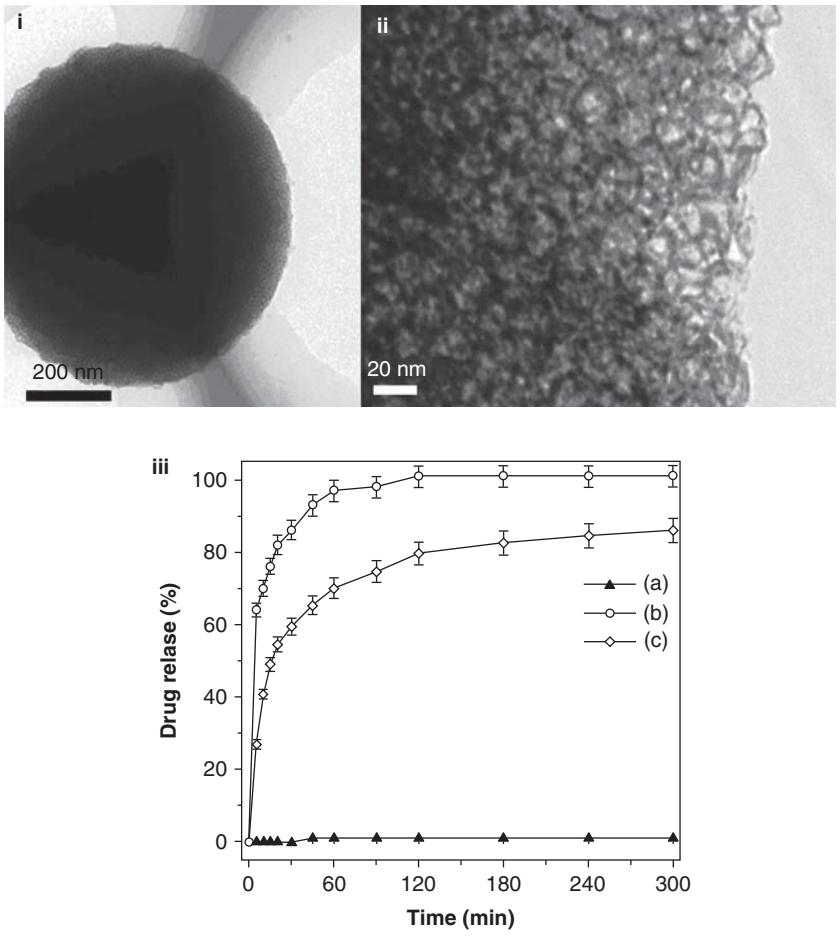

Figure 3. i) SEM micrograph of MCF ii) TEM micrograph of MCF and iii) dissolution profiles of TEL from (a) pure crystalline TEL, (b) TEL–MCF and (c) TEL–SBA-151 in enzyme-free simulated intestinal fluid (pH 6.8).

Reproduced with permission from [37].

MCF: Mesocellular foam; SEM: Scanning electron microscopy; TEL: Telmisartan; TEM: Transmission electron microscopy.

of dissolution and also exhibited superior dissolution characteristics to commercial furosemide tablets.

Inorganic nanoparticles can also be used with the kneading method, as in the case of solvent evaporation. The dissolution rate of a surface SD of the poorly water-soluble drug aceclofenac (BCS class II) using Avicel 200 and Sylysia 350 as polymers was prepared by the kneading method, using different ratios of aceclofenac and polymers. Solid-state study showed partial interaction between aceclofenac and the polymer. *In vitro* dissolution rate of aceclofenac from SD was significantly higher compared to pure aceclofenac. The dissolution rate of the drug was affected by the nature and amount of polymer used. The dissolution rate of aceclofenac–Avicel 200 SD (1:5) was higher than that of aceclofenac–Sylysia 350 SD (1:3) [42]. The enhancement of the dissolution of aceclofenac from SD can be ascribed to several factors, such as lack of crystallinity, particle size reduction, reduction of interfacial tension between hydrophobic drug and dissolution medium, increased wettability and effective surface adsorption of drug on hydrophilic carrier (i.e., surface SD is formed). Avicel 200 (size of particle-180 μm) has a large surface area and can absorb a large amount of drug. During dissolution studies, the immediate sinking of the particles was noted, whereas the untreated drug floated on the surface of the dissolution medium for a longer time.

Kneading method is appropriate to prepare enhanced drug solubilities using β-CD as a drug carrier. For example, it was reported that the dissolution of etoricoxib was notably increased as compared to the pure drug as well as its physical mixture after kneading with β-CD [43]. The complex showed > 75% drug released at 30 min. This is because the interior of the β-CD cone is hydrophobic, due to the presence of glycosidic ether oxygen, and thereby provides a lipophilic microenvironment. Drug can enter in this cone and can be partially or fully included without covalent bonding, while the outer hydrophilic environment contributes to drug dissolution. However, in most cases the dissolution enhancement of the drug was attributed to the formation of drug inclusion

complexes, as in the case of gliclazide or cilostazol drugs [44]. The solid inclusion complexes of gliclazide and β-CD were prepared at a molar ratio of 1:1 and 1:2 by mixing, kneading and co-precipitation methods, both on a small and large scale. Drug content studies, infrared spectroscopic studies, X-ray diffractometry studies and *in vitro* dissolution data indicated that inclusion complexes prepared by kneading method in 1:2 molar ratios were suitable for improving the solubility of gliclazide. This was because inclusion complex formation takes place at the molecular level. Functionalized β-CD, like HP-β-CD, can also be used with better results than neat β-CD [45]. The increment in drug dissolution from nicardipine–HP-β-CD system was higher than nicardipine–β-CD system due to greater water solubility, higher amorphizing, wetting, solubilizing and complexing power in solid state of HP-β-CD towards nicardipine. Enhancement of dissolution with kneaded product was attributed to local solubilization action of the carrier which improved drug wettability and/or solubility and *in situ* formation of readily soluble complexes in the dissolution medium. Similar findings were reported when methyl-β-cyclodextrin (M-β-CD), with an average degree of substitution of 0.5, was used for inclusion complex formation of omeprazole drug, instead of β-CD [46].

During SD preparation with the kneading method, additional additives can be used together with the main polymers, which can have a synergistic effect on drug dissolution enhancement. In a recent study, the improved solubility of a poorly water-soluble drug, norfloxacin, was achieved by incorporating solubilizing additives, such as ascorbic acid and citric acid, into the β-CD complexes [47]. Norfloxacin, being amphoteric in nature, exhibits a higher solubility at pH below 4 and above 8. Addition of substances such as ascorbic acid and citric acid in β-CD complexes reduces the pH of the immediate microenvironment of the drug below pH 4. The results showed an enhanced drug dissolution rate.

Compared to other techniques for the preparation of SDs, it was found that the kneading method is not effective for silymarin drug dissolution enhancement [48]. Statistical evaluation suggested enhancement of silymarin dissolution in co-precipitation (2.5-fold) > spray drying (1.9-fold) > kneading (1.5-fold). This was because in this case the kneading method was not so effective to reduce drastically the drug particle sizes or prepare completely amorphous formulations.

2.3 Wet milling

The common technique for the preparation of micron-size drugs is the mechanical combination (e.g., by crushing, grinding and milling) of larger drug particles. Most of the mills currently used to reduce particle size are dry mills, such as rod mills, hammer mills or jet mills. However, the particle size of drugs produced by dry mills is 1 – 10 μm at best and it is difficult to reduce particle size to a submicron level using this type of equipment [49]. In spite of the widespread use of this technique, the milling process does not represent the ideal way for the production of small particles because drug substance properties and surface properties are altered in a mainly uncontrolled manner. Wet-milling technique is one of the most efficient ways to generate submicron drug crystals and to improve dissolution rate and oral bioavailability [50,51]. The thermal energy generated during wet milling using zirconium oxide balls with a diameter of 0.5 mm is lower than that generated by dry mills because drugs are suspended in organic and, most probably, in aqueous solution. According to this procedure, large micron size drug crystals are wet milled in the presence of a grinding media and a surface modifier. The surface modifiers include various polymers, such as PEG, HPC, HPMC, PVP, low-molecular mass oligomers, natural products and surfactants, pluronic F68, pluronic F108 and lecithin. For drug crystals, wetting water can be used, which can also dissolve the used surfactants. The resulting suspension is wet milled with the grinding media. High-energy-generated shear forces and the forces generated during impact of the milling media with the solid drug provide the energy to fracture drug crystals into nanometer-sized particles. The particle size of the starting materials is typically 100 – 350 μm and after wet-milling process final products with particle sizes < 300 nm can be produced. Processing temperatures are commonly < 40°C. The presence of a surfactant or polymeric carrier and mainly the evolved interactions are very essential for the preparation of crystalline drug nanoparticles or amorphous SDs. Several techniques have already reported concerning wet milling such as high speed homogenization and high pressure homogenization. Using wet-milling procedure several commercial products, such as Rapamune® (sirolimus), Emend® (aprepitant), TriCol® (fenofibrate) and Megace® ES (megestrol), have been commercialized by using a proprietary wet-milling technology, NanoCrystal®.

The main drawback of this procedure is the extended time that is needed, usually > 3 – 4 days, to produce particles sizes < 150 – 300 nm starting from materials with sizes typically 100 – 350 μm [52]. After 4 days of milling, nanosuspensions of piposulfan and etoposide with a mean diameter ~200 nm were harvested. In the case of camptothecin and paclitaxel, milling was continued for an additional 3 – 4 days to further reduce the particle size. The mean diameter for all formed drug nanocrystals ranged between 200 and 250 nm. This is a time consuming procedure and, furthermore, some thermally sensitive drugs may decompose during wet milling from the heat generation. For this reason, Ultra Apex Mill was used recently in order to produce nanopowders of poorly water-soluble and heat labile model drugs (**Figure 4**) [53]. Omeprazole, albendazole and danazol were selected as model drugs. Using Pluronic F-108 or F-68 as dispersing agents, slurries containing drug particles having nanometer size were obtained for all model drugs tested. Although some drugs having crystalline polymorphisms may require lower slurry temperatures than those used in this study, applications of the ULTRA APEX MILL to generate nanopowder drug formulations could be useful in the pharmaceutical industry. These crystal nanoparticles have higher dissolution rates compared with the common larger drug crystals.

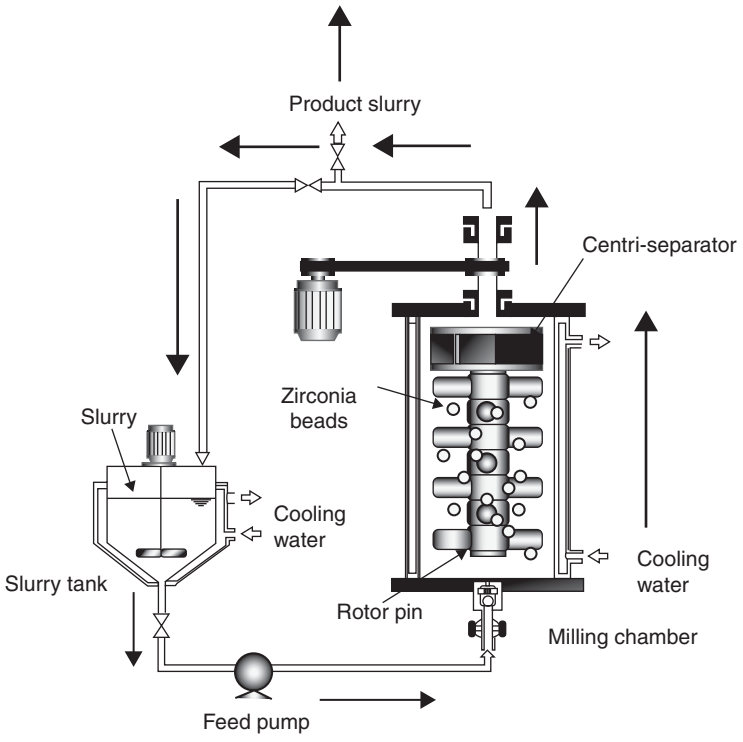

Figure 4. Wet-milling process by ULTRA APEX MILL shown in schematic representation.
Reproduced with permission from Pharmaceutical Society of Japan [53].

During wet milling, amorphous or CSDs can also be prepared. It is well known that amorphous drugs have higher solubilities compared to crystalline. Moreover, it was reported that with the wet-milling procedure, drug nanocrystals formulations can be prepared with increased dissolution rates. Polymer/drug nanocrystalline formulations of itraconazole (ITZ) were made by wet milling (i.e., wet-milled ITZ) in comparison with amorphous nanostructured aggregates (ITZ:mannitol:lecithin = 1:0.5:0.2, weight ratio) which were made using an ultra-rapid freezing process (i.e., URF–ITZ) [54]. Dissolution tests revealed that the extent of supersaturation was 4.7-times higher for URF–ITZ versus wet-milled ITZ, though their dissolution rates were similar. Pulmonary delivery of the nanoparticulate amorphous ITZ composition resulted in significantly higher systemic bioavailability than for the nanocrystalline ITZ composition as a result of the higher supersaturation that increased the permeation. For an aqueous colloidal dispersion of amorphous nanoparticulate ITZ, rapid dissolution produced a supersaturation ~ 4.7-times larger than for a dispersion of crystalline nanoparticulates made by wet milling with the same composition and similar particle surface area. The aerodynamic diameters for both dispersions were suitable for deep lung delivery by nebulization and similar to values produced for pure water. However, the increase in the systemic bioavailability for the amorphous versus crystalline dispersion of about 3.8 was approximately the same as the increase in supersaturation measured *in vitro* in the simulated lung fluid. The experimentally observed similarity in the values of bioavailability and supersaturation would be predicted for a permeability controlled model, where dissolution is very rapid. The high supersaturation, favored by rapid dissolution of amorphous nanoparticles, prior to particle clearance or crystallization, favors the high permeability into the bloodstream.

Tranilast (TL) is an anti-allergic agent and widely used in the clinical treatment of bronchial asthma, atopic rhinitis, atopic dermatitis and keloids. However, the therapeutic potential of TL could be partly limited because of its poor solubility, bioavailability and photostability. To overcome these drawbacks, CSD of TL (CSD–TL) was prepared by the wet-milling technique with the aim of improving physicochemical and pharmacokinetic properties [55]. TL particles in CSD–TL appeared to be crystalline with a diameter of 122 nm, and CSD–TL exhibited marked improvement in the dissolution behavior as compared to crystalline TL. Crystalline TL and PM–TL exhibited poor dissolution/dispersion rates in water, and amounts of dissolved TL from the TL and PM–TL at 60 min were found to be about 10 and 19%, respectively. From these data, the slight improvement of the dissolution properties of PM–TL suggested that HPC-SL itself might have acted as a weak solubilizer in the present formulations, contributing to the limited increase of drug dissolution, as well as prevention of drug aggregation. In contrast, CSD–TL

demonstrated the accelerated dissolution behavior, as evidenced by a release of ~ 97% TL from CSD–TL at 10 min.

Except nanocrystalline SDs, amorphous SD formulations can also be prepared by wet milling, as in the case of Cyclosporine A (SD-CsA), using various polymers, such as HPC (SSL), HPC(L), HPC(H), MC, HPMC, PVP(K30), PVP (K90) and pullulan [56]. For preparation, CsA was micronized with zirconia beads in various polymer solutions and freeze dried to provide an SD formulation of CsA with an overall yield of 90% or higher. SEM micrographs (**Figure 5**) of crystalline/amorphous CsA and HPC(SSL)-based SD formulation revealed clear changes in the morphology of the powder particles after wet milling, owing to the evident formation of SD. There was significant improvement of dissolution/dispersion behavior of some SD formulations, especially CsA-loaded SD using water-soluble polymers with low-molecular mass and viscosity, such as hydroxypropyl cellulose. A rapid dissolution behavior was found compared to a physical mixture of amorphous active pharmaceutical ingredient (API) and one of the above mentioned excipients.

Polymer drug interactions evolved during wet milling are also important for efficiently increase of dissolution rates. Suspensions of nifedipine, a practically water-insoluble drug, were prepared in the presence of a biocompatible polymer, PVP (K value 17) and three surfactants, sodium lauryl sulfate (SLS, anionic), cetyltrimethylammonium bromide (CETAB, cationic) and polysorbate 80 (Tween 80, nonionic), by wet milling in ceramic ball mills [57]. Particle size analysis indicated that milling of suspensions in solutions of PVP and surfactants was an efficient method for reducing the particle size of nifedipine to below 10 μm. Furthermore, DSC and XPS analysis indicated that during milling the nifedipine crystals were coated with the PVP or surfactants and that milling with PVP stabilized the nifedipine crystal form during milling, while nifedipine was gradually amorphisized when milled in a quaternary nifedipine–PVP–SLS–CETAB system. The decrease in particle size caused a significant decrease in sedimentation rate and increased the dissolution rate of nifedipine in simulated gastric fluid when compared to milled nifedipine and powder mixtures of the drug and the excipients.

Oral bioavailability of an immediate release tablet containing wet-milled crystals of the poorly water-soluble drug, cilostazol, and establishment of *in vitro–in vivo* correlation were investigated by Jinno *et al.* [58], Submicron sized cilostazol (median diameter: 0.26 μm) was successfully prepared using a beads mill in water in the presence of a hydrophilic polymer and an anionic surfactant. The milled suspension was solidified with a sugar alcohol, as a water-soluble carrier, by spray-drying method. The co-precipitate was compressed into an immediate release tablet with common excipients. Oral bioavailability of the wet-milled cilostazol tablet in male beagle dogs was 13-fold higher than the hammer-milled commercial tablet in fasted condition.

Wet milling followed by a spray-drying procedure as described before was also mentioned recently [59]. Sparingly water-soluble drugs such as candesartan cilexetil offer challenges in developing a drug product with adequate bioavailability. However, the bioavailability of candesartan cilexetil is dissolution-limited following oral administration. To enhance bioavailability and overcome variability in systemic exposure, a nanoparticle formulation of candesartan cilexetil was developed. Candesartan cilexetil nanoparticles were prepared using a wet bead-milling technique. The milled nanosuspension was converted into solid intermediate using a spray-drying process. The nanosuspensions were characterized for particle size before and after spray drying. The spray-dried nanoparticles were blended with excipients for tableting. This study demonstrated that tablet formulation incorporating drug nanoparticles showed significantly faster rate of drug dissolution in a discriminating dissolution medium, as compared to a commercially available tablet formulation. Systemic exposure studies in rats indicated a significant increase in the rate and extent of drug absorption.

As an evolution in the above described wet-milling procedures, a novel approach of nanosizing a drug–polymeric complex, in order to increase both solubility and dissolution rate of poorly water-soluble drug, was investigated by Dai *et al.* [60]. According to this a hydrophilic polymer, λ-carrageenan, was first complexed with a model poorly water-soluble compound, in order to increase the compound's aqueous solubility. The compound–carrageenan complex was further nanosized by wet milling to enhance the dissolution rate. By complexing with carrageenan, the compound became amorphous in the complex. Using additional carrageenan as a stabilizer for nanosizing, a nanosuspension of a compound–carrageenan complex with a median particle size of about 0.3 μm was successfully developed. The particle size of the nanosuspension did not increase significantly during the lyophilization process and was stable for at least 39 days at room temperature after lyophilization. This approach of nanosizing a drug–carrageenan complex increased the aqueous solubility of the compound from < 1 to 39 μg/ml. In addition to increasing aqueous solubility, the nanosized compound–carrageenan complex had a faster dissolution rate than the complex, the free compound and the nanosuspension of the free compound.

2.4 Spray drying

Spray drying is a well-established method for processing solutions, emulsions and suspensions into powders, efficiently controlling the size, density and morphology of the particles. In addition, the method is cheap, fast and a one-step process, which is why it has been used in numerous applications in pharmaceutical formulations. Typically, spray-dried powders (SDPs) are amorphous in nature due to their rapid solidification. Spray drying has been largely applied in the food and pharmaceutical industries for the preparation of fine powdered forms, such as micro-encapsulated APIs. Spray drying is also used extensively for the preparation of drug SDs [61-64].

The solvents used to dissolve the drug and the excipients for spray drying could significantly affect the properties

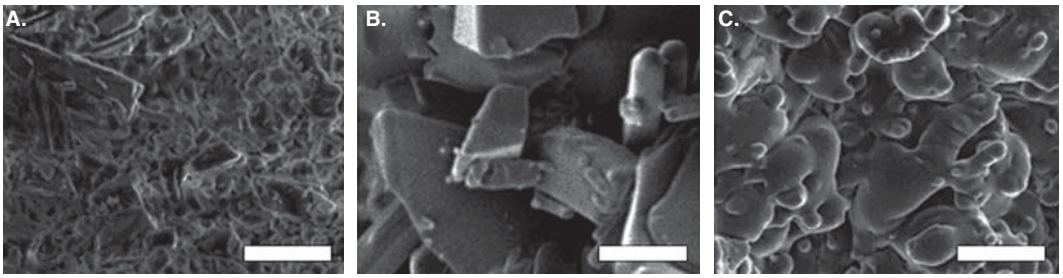

Figure 5. Scanning electron microscopic images from CsA samples, including (A) crystalline CsA, **(B)** amorphous CsA and **(C)** SD of amorphous CsA with HPC(SSL) (SD-CsA–HPC(SSL)). Each bar represents 5 μm.
Reproduced with permission from [56].
CsA: Cyclosporine A; SD: Solid dispersion.

of the SDs [65]. The stability and dissolution rate of the ternary SD of griseofulvin, PHPMA and PVP were found to behave differently when the solvent system was changed from acetone–water to acetone–methanol. These differences were attributed to interactions of the linking molecule (PHPMA) with the solvent system. Another factor which was found to influence the properties of the SD is the concentration of the drug and the polymers in solution (before spray drying). More diluted solutions, while maintaining constant ratio of drug:polymers, resulted in the formation of smaller particles with slower relaxation of the amorphous form. The small size resulted in increased water uptake, which affected the stability, despite the slower relaxation at dry conditions. These results demonstrate the importance of controlling the spray-drying conditions to prepare SDs with improved stability and dissolution properties.

The used carriers affect mainly the crystallinity of the drug in SDs. For example, SDs of sibutramine drug with improved solubility and bioavailability were prepared with water, HPMC, poloxamer and citric acid using spray-drying technique [39]. The sibutramine base-loaded SD gave two type forms. Like a conventional SD system, one type appeared as a spherical shape with smooth surface, as the carriers and drug, with a relatively low melting point, was soluble in water and formed it. The other appeared as an irregular form with a relatively rough surface. Unlike conventional SD system, this type changed no crystalline form of drug. The results suggested that this type was formed by attaching hydrophilic carriers to the surface of drug without crystal change, resulting from changing the hydrophobic drug to hydrophilic form. The sibutramine-loaded SD at the weight ratio of sibutramine base:HPMC:poloxamer:citric acid of 5:3:3:0.2 gave the maximum drug solubility of about 3 mg/ml. Furthermore, it showed similar plasma concentration, the AUC and C_{max} of parent drug of metabolite I and II in the commercial product, indicating that it might give similar drug efficacy compared to the sibutramine hydrochloride monohydrate-loaded commercial product in rats. Thus, this SD system would be useful to deliver poorly water-soluble sibutramine base with enhanced bioavailability.

Cefpodoxime proxetil (CP) is a prodrug, third generation cephem-type broad spectrum antibiotic administered orally. However, CP was found to be a poorly water-soluble drug with low bioavailability when orally administered. In a recent investigation, the spray-dried CP nanosuspension (SDN) was prepared [66]. Formation of the nanosuspension maintains the poorly soluble drug at reduced particle sizes and this apparently increases the dissolution rate and, therefore, improves the bioavailability. The pharmacokinetic study of SDN, in comparison to a marketed CP for oral suspension (MS), was performed in rabbits after a single oral dose. It was found that SDN exhibited a significant decrease in t_{max}, a 1.6-fold higher AUC and a 2.33-fold higher C_{max} than MS.

The feasibility of α-glucosyl hesperidin (Hsp-G) to improve the dissolution and bioavailability of poorly water-soluble drug was investigated. An SDP of Hsp-G and flurbiprofen (FP), an acidic drug (pK_a = 3.78) with low water solubility, was prepared by a spray-drying method [67]. Powder XRD analysis revealed the conversion of FP from the crystal to the amorphous form when dispersed in Hsp-G. The SDPs of FP–Hsp-G resulted in pronounced improvement of both the dissolution rate and solubility of FP. The apparent solubility of FP in hydrochloric acid solution (pH 1.2) was improved 10-fold more than untreated FP crystals when prepared as SDPs in Hsp-G. The bioavailability of FP from the prepared SDPs was evaluated *in vivo* after oral administration to rats, in comparison with the untreated FP crystals. The results revealed a 2.5- and 2.8-fold improvement of the C_{max} and AUC values, respectively, after oral administration of the SDPs of FP–Hsp-G. In conclusion, Hsp-G is a potentially safe material to enhance the dissolution and absorption of poorly water-soluble drugs. Although FP crystals had an amorphous form in the spray-dried system with HPMC in our report, the dissolution amount of FP from SDPs of FP–HPMC was dramatically lower than that with Hsp-G. This result indicates that, in the case of FP, changing the physical form of the drug from the crystalline to the amorphous form and utilization of a spray-drying system had little impact on the solubility of FP. A plausible explanation for the significant enhancement of apparent solubility of FP may be a

specific structure of FP and Hsp-G in aqueous medium, by which FP existed and solubilized in the special structure.

The above mentioned studies used the typical spray-drying technique. However, in order to increase the performance of the prepared SDs, in recent years spray drying has been used simultaneously with other techniques. For example, spray-freeze drying (SFD) of oleanolic acid (OA) with PVP-40 as stabilizer, sodium caprate (SC) as wetting agent and penetration enhancer produced kinetically stable, amorphous SD systems with superior *in vitro* dissolution performance [68]. Inclusion of SC coupled with the replacement of OA with its sodium salt (OA-Na) in the formulation was shown to substantially decrease the observed absorption variability. These results suggested that increases in both dissolution rate and intestinal permeability of such drugs, as exemplified by the SFD-processed dispersion system containing both OA-Na and SC, are critical to reducing the large inter-individual absorption variability commonly observed with this class of drugs. SDs of a poorly water-soluble drug piroxicam in PVP were prepared by precipitation with compressed antisolvent (PCA) and spray-drying techniques [69]. Piroxicam was found amorphously dispersed in both SD systems with a drug to polymer weight ratio of 1:4. By comparison, PCA-processed SDs showed distinctly superior performance in that piroxicam dissolved completely within the first 5 min and the dissolution rate was at least 20 times faster than the raw drug within the first 15 min. From this study, it was found that the PCA technique is capable of preparing SDs with faster dissolution because of the smaller size of its products compared to the spray-dried sample.

In all these apparatus, the feed material is atomized through a spray nozzle at high pressure with high mechanical shear forces. The atomization and application of heat are separate functions in space and time, and the heat transfer rate is lower and less turbulent, leading to longer drying times and higher maintenance costs, such as gas and electrical inputs. The pulse combustion dryer system is a relatively new apparatus for drying which generates powerful shock waves via its pulse engine, effectively breaking up a solid liquid [70]. Combustion air and gaseous fuel are drawn into the pulse combustion chamber and form a fuel–air mixture, which is ignited by a pilot and explodes, creating hot, high-pressure gases. Most of the hot gases form shock waves and rush down the tailpipe toward the atomizer. Then, more fuel and air enters and explodes again due to the hot gases left in the tailpipe. This combustion cycle repeats itself at a frequency of about 50 – 1000 Hz to produce consecutive high-temperature shock waves. Next, the feed material is sprayed by the atomizer into the high-speed combustor exhaust gases produced by the pulse engine and is dried by the actions of shock waves, ultrasonic waves (greater than 155 dB), gas flow and gas temperature (200 – 300°C) in the drying chamber. Finally, the dried powders are retrieved using collection equipment, such as a cyclone and bag filter. The pulse combustion dryer system can offer important advantages over spray drying as pulse combustion drying is accomplished by the application of not only heat for evaporation, but also the mechanical action of gas dynamic atomization, providing an environment of extreme turbulence that promotes very high rates of heat transfer and dehydration through compression and contraction. By using this system, SDs of nitrendipine (NTD), a poorly water-soluble drug, were prepared with the Hypulcon pulse combustion dryer system (**Figure 6**), and the physicochemical properties of particles were investigated and compared with those of particles prepared with a usual spray dryer. The SD particles prepared with Hypulcon using Aerosil and Tween 80 as carriers showed improved properties over those prepared with a conventional spray dryer, such as smaller particle size, tighter particle size distribution and no agglomeration. Powder XRD and DSC evaluation showed that the drug in the NTD–Aerosil SD prepared with a 5% (v/v) Tween 80 solution was dispersed in an amorphous state. FTIR spectroscopy indicated the presence of hydrogen bonds between NTD and Aerosil. Aerosil had a greater ability to improve the dissolution of NTD than Sylysia and other polymers. The good hydrophilicity and dispersibility of Aerosil, solubilization of Tween 80, and actions of shock waves and ultrasonic waves might account for the amorphization of NTD and improved dissolution rate of the SDs.

Evolution of the spray dryers has also been observed at the spray drier nozzles. Multi-fluid nozzles were used in a recent study consisting of three feed tanks for three fluids and one for the compressed air line [71]. Thus, three sample solutions can be fed simultaneously. Such a spray drier with a modified multi-fluid nozzle was used to prepare microparticles of a poorly water-soluble antimalarial drug, artemisinin (ART), with the aim of improving its dissolution in water [71]. ART was co-spray dried with a hydrophilic polymer, PEG. The DSC and XRD studies showed that the crystallinity of ART decreased after spray drying. The dissolution of ART from the spray dried ART–PEG composites was more rapid than that from their respective physical mixture and the original ART powder. For example, the dissolution of ART from the spray dried ART–PEG composite (1:6) was 6.5 times higher than that from the original ART powder during the first 30 min.

Spray-freezing into liquid (SFL) was also used some years ago, which involves the atomization of a feed liquid containing a poorly water-soluble or insoluble API and solubility enhancing excipients directly into a cryogenic liquid (liquid N_2) to produce a frozen micronized powder that is subsequently dried [72]. *In situ* formation of a flowable powder with the API molecularly dispersed in a micronized excipient matrix occurs during SFL processing. The advantages of the SFL process result from the URF rates achieved by atomizing the feed solution beneath the cryogenic liquid surface. URF rates prevent phase separation of the API and excipient carrier and crystalline growth of frozen water, both of which would result in non-homogeneous powder aggregates consisting of crystalline API domains. Instead, URF rates produce a porous micronized

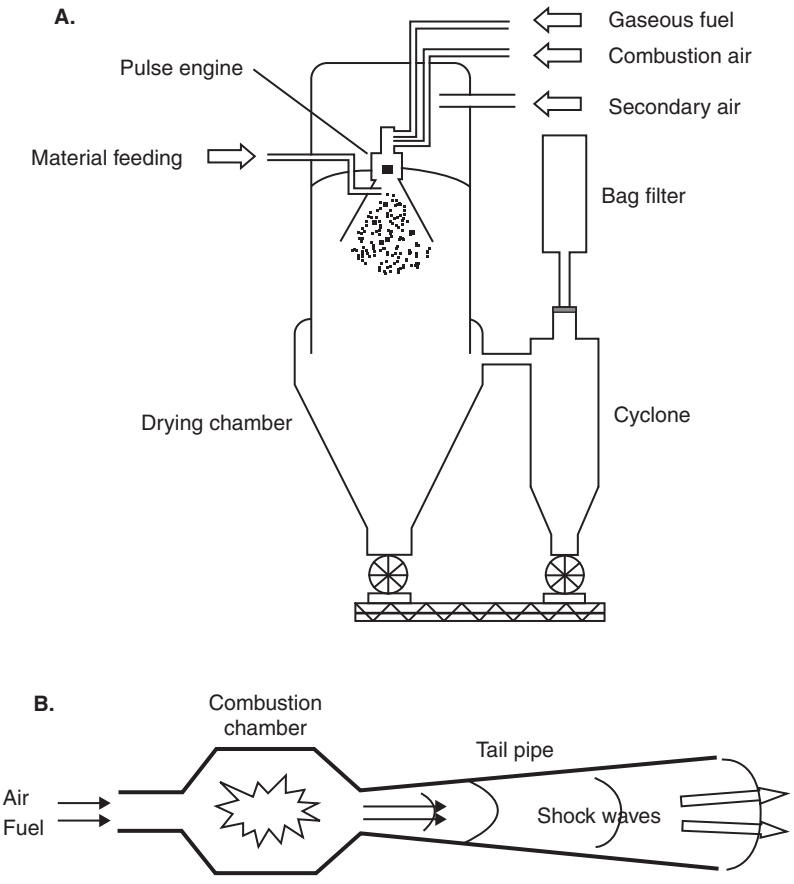

Figure 6. Scheme of Hypulcon pulse combustion dryer system (**A**) and Pulse engine (**B**).
Reproduced with permission from [70].

flowable powder with a high surface area and amorphous API stabilized in an excipient matrix. Because SFL micronized powders have high surface areas and contain amorphous danazol, enhanced dissolution of poorly water-soluble or insoluble APIs in aqueous media is achieved.

2.5 Cyclodextrin complexation

CDs comprise a family of cyclic oligosaccharides, consisting of (α-1,4)-linked α-D-glucopyranose units with a lipophilic central cavity. The three natural CDs molecules with pharmaceutical applications, α-, β- and γ-CDs, contain 6, 7 and 8 glucose units, respectively, in a ring, creating a cone-like shape. β-CD is widely used in pharmaceutical applications due to its availability and cavity size, suitable for host of a widest range of drugs. CDs are used industrially in pharmaceutical applications. The interior of the CD cavity is considerably less hydrophilic than the exterior aqueous environment and can, thus, host less hydrophilic guest molecules. In contrast, the exterior surface is sufficiently hydrophilic to give CDs high aqueous solubility. CDs may increase the solubility of highly insoluble drugs up to several thousand-fold, compared to the aqueous solubility of the drug alone [73-76]. This occurs as a result of the formation of an inclusion complex, in which the guest and host molecules are in dynamic equilibrium (**Figure** 7). These complexes form aggregates in aqueous solutions, which are able to solubilize lipophilic water-insoluble drugs through non-inclusion complexation or micelle-like structures [73-78]. The main drawback of CD-based drug delivery is the 1:1 stoichiometric ratio that can result in a low drug-carrier weight ratio [77].

Except for the complex formation between CDs and drug, CDs were used as protective stabilizers for the preparation of surfactant-free nanocrystals of IMC, by using the emulsion solvent diffusion method [79]. Submicron-sized particles of IMC with average diameters in the range of 300 – 500 nm were obtained by incorporating α-, β- or γ-CD in the outer phase of the primary emulsions. Quantitative determination demonstrated that > 80% of IMC was recovered as fine particles smaller than 0.8 μm. XRD diffraction and DSC analysis of the freeze-dried samples confirmed the polymorphic change of IMC to the metastable form. A significant enhancement of the dissolution rate of IMC nanocrystals was observed when compared to the commercial powder.

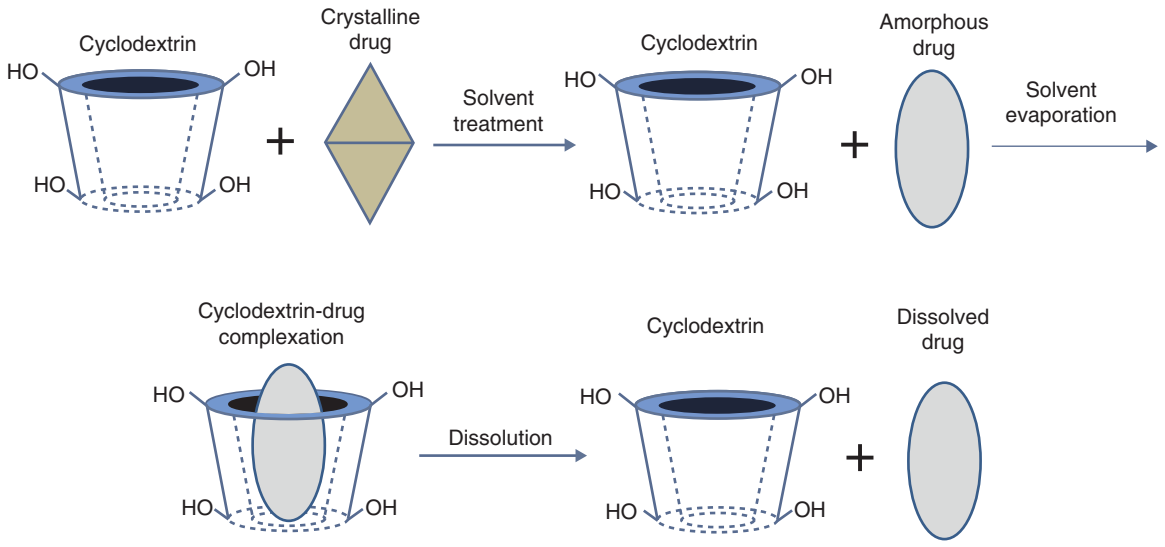

Figure 7. Drug complexation in cyclodextrins.

In most of the above reported studies, the CDs–drug SDs were formed with solvent evaporation and freeze drying. In a recent study, inclusion complexes between ITZ and β-CD were prepared using simple physical mixing, conventional co-precipitation method and supercritical carbon dioxide ($SCCO_2$), for comparison purposes [80]. Results showed that temperature, pressure and ITZ:β-CD ratio had significant effects on the inclusion yield of the complex prepared by the $SCCO_2$ method. Higher inclusion yields were obtained in the $SCCO_2$ method as compared to physical mixing and co-precipitation methods. *In vivo* drug pharmacokinetic studies showed that the ITZ-β-CD product prepared using $SCCO_2$ gave higher bioavailability of ITZ as compared to the products obtained by physical mixing or co-precipitation methods.

Natural CDs, in particular β-CD, are of limited aqueous solubility. As a result, complexes formed via interactions between lipophilic compounds and these CDs may also be poorly soluble, resulting in the precipitation of the solid CD complexes from water and other aqueous systems. For this reason, in some reported studies CDs could not enhance the dissolution rate of a drug [74,81]. Thus, substitution of any of the hydrogen bond-forming hydroxyl groups, even by lipophilic functions, results in dramatic improvement in their aqueous solubility. Hydrophilic CDs, namely HP-β-CD and sulfobutyl ether β-CD (SBE-β-CD), are generally considered to be nontoxic at low to moderate oral and intravenous doses. In addition, human experience with CD derivatives, specifically SBE-β-CD and HP-β-CD, indicates that these two CDs are well tolerated by humans and have no adverse effects on the kidneys or other organs, following either oral or intravenous administration. In a recent study, it was verified that these derivatives are more appropriate for drug dissolution enhancement [82]. In similar poorly water-soluble drugs, such as curcumin, it was found that the ability to increase its solubility by CD increased in the order of HP-β-CD > M-β-CD > β-CD > γ-CD [83]. This is because curcumin molecules with bulky side groups on the phenyl moiety seemed to fit better into the HP-β-CD cavity than into the cavities of M-β-CD. Curcumin seems to be better included in HP-β-CD with a very significant increase in solubility exhibited when compared to the pure drug.

HP-β-CD has superior properties (a highly soluble, amorphous powder with no detectable oral toxicity) as a pharmaceutical additive. HP-β-CD can modify the release rate of poorly water-soluble drugs, which can be used for the enhancement of drug absorption across biological barriers, serving as a potent drug carrier in immediate release formulations [84] and being useful for inhibition of polymorphic transition and crystallization rates of poorly water-soluble drugs during storage, which can consequently maintain the higher dissolution characteristics and oral bioavailability of the drugs [85]. IMC was used as a model drug and SDs containing IMC and HP-β-CD at a 1:1 w/w ratio were manufactured by both melt extrusion process and wet extrusion process [86]. The dissolution rates of IMC from extrudates manufactured by melt extrusion and wet extrusion with HP-β-CD were significantly higher than those of the physical mixture of IMC and HP-β-CD. In extrudate manufactured by melt extrusion, γ-form of IMC changed to a completely amorphous form during melt extrusion, due to heating above the melting point of IMC. On the other hand, in extrudate manufactured by wet extrusion, γ-form of IMC changed to an amorphous form partially due to interaction between IMC and HP-β-CD and mechanical agitating force during process. Application of HP-β-CD in extrusion process is useful for the enhancement of dissolution rate for poorly water-soluble drugs.

Further advantages in drug solubility can be obtained by the use of a double-loading technique, that is, by preparing liposomes loaded with the plain drug in the lipophilic phase and its CD complex in the aqueous phase of the vesicles, so as to obtain both a fast onset action and a prolonged effect. Such a combined approach of CD complexation and entrapment in liposomes was investigated to develop a topical formulation of local anesthetics [87]. For both benzocaine and butamben, HP-β-CD was a better partner than β-CD; drug–HP-β-CD co-evaporated products showed the best solubility and dissolution properties, and were selected for loading into liposomes.

3. Conclusions

To increase the bioavailability of poorly water-soluble drugs, researchers and the pharmaceutical industry focused on developing new methods or improving the already extensively used. Traditional methods for the preparation of SDs, such as solvent evaporation, kneading and wet milling, disperse drugs in the liquid phase by surface active agents and are extensively used nowadays for the dissolution rate enhancement of poorly water-soluble drugs. The already presented literature on this field reveals many interesting aspects, such as used of alternative techniques, combination of solvents, different carriers, new apparatuses and technologies. Some of these are quite interesting. As can be seen, all the used strategies and the evolution of these methods focus on decreasing the drug particles or on preparing amorphous formulations. SDs, in which the drug is suspended in nanocrystals or in an amorphous state in a hydrophilic polymer matrix, are favored over most other methods concerning dissolution rate enhancement of poorly water-soluble drugs. Drug complexation in CD cavities is also an able and dynamic method to solubilize lipophilic water-insoluble drugs.

4. Expert opinion

'SD' is one of the earlier, yet still favorable, approaches for overcoming drug dissolution and increase solubility of poorly water-soluble drugs. Owing to its simplicity from the manufacturing and process scalability standpoints, SD has become one of the most active and promising research areas of great interest to pharmaceutical companies. For this reason, the research papers in the area increase at a stable rate (**Figure 8**) and this subject is of the highest priority for the scientific community and pharmaceutical companies. Thus, even though the numbers of pharmaceutical products on the market based on SDs are limited due to stability problems and difficulties with manufacturing, in recent years are steadily increasing. The strategy attempts to modify the dissolution kinetics by dispersing the drug as small solid particles in an inert carrier, aiming at increased surface:volume ratio, which increases solvent access. The progresses that have been made in recent years on SDs prepared by several techniques such as solvent evaporation, kneading, wet milling, spray drying and CD complexation, the effect of evolved interactions in physical state of the drug and formulation stability during storage, the characterization of the physical state of the drug and the mechanism of dissolution rate enhancement are discussed in the present part of this extended review. In the second part, a lot of different methods are presented and discussed, such as melt mixing, supercritical methods, electrospinning, usage of inorganic nanoparticles such as layered double hydroxide, silicon dioxide and mesoporous silica, nanocomposites and microwave irradiation, in order to cover almost all the methods used for SD preparation [88].

The interactions between the drug and polymer, during SD preparation, and their extent are responsible for the formation of amorphous or crystalline dispersions and, possibly, for the particle size distribution of the drug into the polymer matrix. It is accepted nowadays that the glassy state of a drug compound dispersed in such polymer matrices is the most desired state, as it improves dissolution rates and hence drug absorption. Despite the large number of published studies on SDs (> 3000), the nature of the drug's amorphous state has been only recently completely investigated [22,23,29,30]. In most of the published papers on SDs, when the drug was dispersed in amorphous state it was believed that it was completely miscible with the polymer matrix and was dispersed in a molecular level. This statement was based on DSC experiments, wherein in such SDs only one glass transition temperature was detected, ranging between that of the drug and polymer matrix. However, in recent years, a combination of different techniques, such as DSC, dynamic thermomechanical analysis, SEM, TEM and micro-Raman, proved that except the molecular dispersion the drug is also dispersed in amorphous nanodispersions [22,23,29,30]. The size of these is directly dependent on the polymer:drug ratio and ranges between 30 and 100 nm, at drug concentrations 10 – 20 wt %, and up to 500 and 1000 nm at saturated concentrations, such as 50 wt% [29,30].

Significant progress has also been achieved in recent years on optimizing the used methods in the manufacture of SDs and the application of new and innovative materials that maximize the benefits of SDs. This is evident in the methods of solvent evaporation and kneading, which are the simplest for the production of SDs. Such materials are inorganic nanoparticles, such as different types of SiO_2, mesoporous silica and spherical MCFs. These nanoparticles have as an advantage their extremely large specific surface areas, ranging between 200 and 1000 m^2/g. Thus, the drug can be dispersed in this surface area at a molecular level or in the form of nanocrystals. A monolayer can also be formed on the nanoparticles' surface, due to the evolved interactions between the silanol surface groups and the reactive groups of the drug. All these result in the substantial increase of dissolution rates and solubility of poorly water-soluble drugs.

In the wet-milling process, drug nanocrystals in the range of 100 – 300 nm or amorphous SDs can be prepared, depending on the used time, temperature and polymer matrices. For the

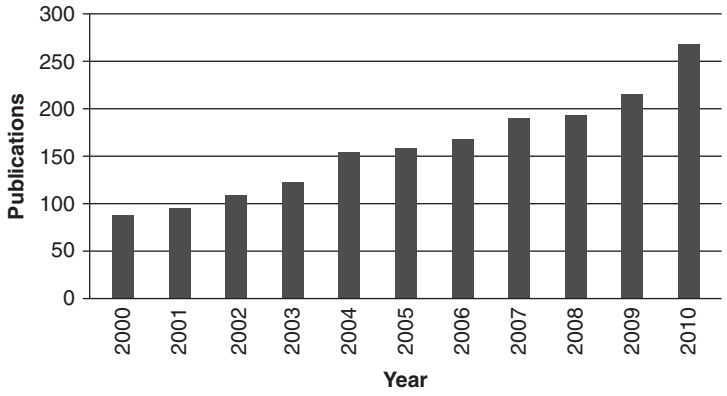

Figure 8. Publications per year on drug solid dispersion formulations.

preparation of drug in fully amorphous state a combination of complexation and nanosized wet milling can be applied. Furthermore, new apparatuses, such as the Ultra Appex Mill were used, preparing drug nanocrystals in the range of 100 – 250 nm. Such nanodispersions are rapidly dissolved.

Spray drying is also one of the oldest and most used methods for the preparation of SDs. However, in recent years this method is further evolving. In order to increase its effectiveness, pulse combustion dryer systems were recently used, taking into account that the applied mechanical action during gas atomization can prepare smaller particle sizes and tighter particle distribution, without the formation of agglomerates. Combination of spray drying with freeze drying or spray freezing into liquid nitrogen can also be used for the preparation of amorphous SDs. Ultra rapid freezing rates prevent phase separation and can produce porous micronized powder with high surface area and, thus, increased drug dissolution rates. Spray dryers with multi-fluid muzzles have also been investigated.

Drug complexation is very effective for dissolution rate enhancement when CDs are used as drug carriers, for the preparation of SDs, and these formulations can be prepared by solvent evaporation, melt mixing, freeze or spray drying and so on. However, it was reported by many researchers that CD derivatives, such as HP-β-CD, SBE-β-CD and M-β-CD, are more effective for the dissolution rate enhancement. This is because it seems that drugs fit better into the derivatives' cavities than of the unmodified's. Furthermore, these derivatives are amorphous, with low toxicity and higher solubility. Double loading techniques preparing liposomes with drug in the lipophilic phase and complexation with CDs can lead to formulations with fast dissolution rates.

From the above review of recent developments and evolution of manufacturing methods of SDs, dynamic development and application of more and more innovative methods are observed. Towards this direction, the technology, development and transfer of new techniques from other applications into the drug manufacturing processes also contribute. These innovations have resulted in the solution of many problems and simplification of manufacturing processes of SDs preparation. Following a decade of developments in SDs, I personally believe that in recent years significant progress has been achieved, which will result in a dramatic growth of prepared commercial products by use of these techniques. Thus, more and more companies, due to the simplicity and effectiveness of these methods, will switch over to them and benefit from the advantages and innovations that they offer. Thermodynamic instability is the main reason why amorphous drugs have not been used widely for the preparation of commercial products. However, in recent years a lot of progress has also been achieved in the stability of amorphous forms of poorly water-soluble drugs in SDs and mainly in understanding the tendency toward crystallization [89]. There are several methods that have been developed to circumvent this problem. It has been shown that physical instability of the amorphous state is linked with molecular mobility. For systems at temperatures well below their glass transition temperature (T_g), where translational and rotational movements are 'frozen', the molecular mobility is highly reduced and the lag time for crystallization is generally very long. However, the maximum crystallization inhibition of a drug in an SD can only be achieved when the drug is dispersed homogeneously or best at the molecular level in the matrix. This suggests that the basis of the selection of the right polymeric excipient for the formulation of amorphous SDs should be the limit of solid state solubility of the drug in the selected polymer. Thus, drug–polymer miscibility and solid solubility of drug in the polymer provide the right estimates of the drug loading to manufacture stable SD formulations [90]. A glassy polymeric matrix restraining favorable intermolecular interactions between the drug substance and the polymer is more favorable. In a recent study, it was found that small amounts of PVP significantly retard re-crystallization of a

drug in SDs [91]. Variation in molecular mobility of PVP is not the dominant factor in determining variation in propensity for re-crystallization from glassy systems and it was suggested that the surface interactions between PVP and drug crystals nuclei are the main reason for this behavior. For this reason, in all used methods for preparation of SDs emphasis should be given to maximize the interactions between polymeric matrix and drug. The key is to choose substrates with appropriate reactive groups that can participate in interactions (ionic or hydrogen bonding) with drugs' reactive groups.

Declaration of interest

The author states no conflicts of interest and has received no payment for the preparation of this manuscript.

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