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REVIEW ARTICLE

Nanoparticle Engineering Processes for Enhancing the Dissolution Rates of Poorly Water Soluble Drugs

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ABSTRACT

Poor water solubility is an industry wide issue, especially for pharmaceutical scientists in drug discovery and drug development. In recent years, nanoparticle engineering processes have become promising approaches for the enhancement of dissolution rates of poorly water soluble drugs. Nanoparticle engineering enables manufacturing of poorly water soluble drugs into nanoparticles alone, or incorporation with a combination of pharmaceutical excipients. The use of these processes has dramatically improved in vitro dissolution rates and in vivo bioavailabilities of many poorly water soluble drugs. This review highlights several commercially or potentially commercially available nanoparticle engineering processes recently reported in the literature for increasing the dissolution properties of poorly water soluble drugs.

Key Words: Nanoparticle engineering process; Poorly water soluble drug; Water insoluble drug; Nanoparticle; Solubility; Dissolution; Bioavailability; Drug delivery; Particle engineering; Wet milling; High pressure homogenization; PCA; SEDS; SAS; RESAS; SFL; EPAS.

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INTRODUCTION

It has been reported that about 40% of the compounds being developed by the pharmaceutical industry are poorly water soluble.[1,2] A limiting factor to the in vivo performance of poorly water soluble drugs after oral administration is their inadequate ability to be wetted by and dissolved into the fluid in the gastrointestinal (GI) tract. Therefore, increasing the dissolution rate of poorly water soluble drugs is an important and significant challenge to pharmaceutical scientists in order to maximize absorption. According to the Noyes–Whitney equation, reducing the particle size and thus increasing the surface area will increase the dissolution rate of poorly water soluble drugs.[3] Commercially used processes for micronization include mechanical milling, recrystallization, solid dispersion, freeze drying, and spray drying.[4–8] However, these processes have limitations that include organic solvent use, thermal degradation, large residual solvent content, and difficulties in controlling particle size and size distribution during processing. These limitations affect drug particle stability, powder flow properties, and efficiency of the delivery system. In particular, further reduction of particle size of poorly water soluble drugs into the nanoparticle range remains challenging.[5,9,10]

Over the last 10 years, nanoparticle engineering processes have been developed and reported for pharmaceutical applications. Purposefully increasing solubility and dissolution rate for these poorly water soluble drugs by increasing surface area using nanoparticle engineering processes is a very promising method for improving drug bioavailability.[5–20] Several reviews discussing particle engineering processes[4–6,9,10,15,16,18,20–26] have been written. The present review will focus on several commercially or potentially commercially available nanoparticle engineering techniques recently reported in the literature for enhancement of dissolution of poorly water soluble drugs. These nanoparticle engineering processes involve the use of mechanical micronization techniques, supercritical fluid processes, cryogenic spraying, and solvent evaporation.

Mechanical Micronization Processes

A common approach used for many years in the pharmaceutical industry is micronization of poorly soluble drugs by milling.[15,21] The standard microparticles produced by milling have a particle size of about 5 μm. The formation of particles below 1 μm is a challenge due to aggregation of high surface area materials. Until now, two mechanical processes were commercialized for nanoparticle preparation. First, the wet milling technique, NanoCrystals® technology, was developed and patented in 1992 by Liversidge et al. and formerly owned by Sterling Drug Inc., later acquired by Elan Corporation.[9,21,27] The second process is a high pressure homogenization process, DissoCubes® technology, which was developed and patented by Müller et al. in 1994 and formerly owned by the Drug Delivery Services GmbH in Germany and is now owned by SkyePharma PLC.[15,21,28]

Wet Milling

Wet milling is an attrition process in which large micron size drug crystals are wet milled in the presence of grinding media and a surface modifier.[27] The rigid grinding media is typically spherical in form, having an average size less than about 3 mm. The grinding media used in the process include zirconium oxide, such as 95% ZrO stabilized with magnesia, zirconium silicate, and other media, such as glass grinding media stainless steel, titania, alumina, and 95% ZrO stabilized with yttrium.[21,27] The surface modifiers include various polymers, low molecular weight oligomers, natural products and surfactants, such as polyvinyl pyrrolidone, pluronic F68, pluronic F108, and lecithin. The particle size of the starting materials is typically less than 100 μm and micronized by a jet-milling process. The particle size of the final product is less than 400 nm.[9,29]

In the wet milling process, the poorly water soluble drug is first dispersed in an aqueous-based surfactant solution, and then the resulting suspension is wet milled with the grinding media. High-energy-generated shear forces and the forces generated during impaction of the milling media with the solid drug provide the energy to fracture drug crystals into nanometer-sized particles.[9,30] Processing temperatures commonly are less than 40°C[27] and processing pressures are up to about 20 PSI. Milling efficiency is dependent on the properties of the drug, medium, and stabilizer. It was reported that a significant reduction in particle size was observed within 24 hours of wet milling.[29,31] Routinely, the drug/surfactant slurry was milled to a final size of less than 400 nm and generally this could be achieved over a 4-day period.

Poorly water soluble drugs in the nanoparticle suspension are reported to be in a crystalline state.[9] Figure 1 shows an electron micrograph and a diagrammatic representation of drug particles formulated as a colloidal dispersion. The insert provides a visual description of the crystalline nanoparticles generated using wet milling. The nanoparticles are typically less

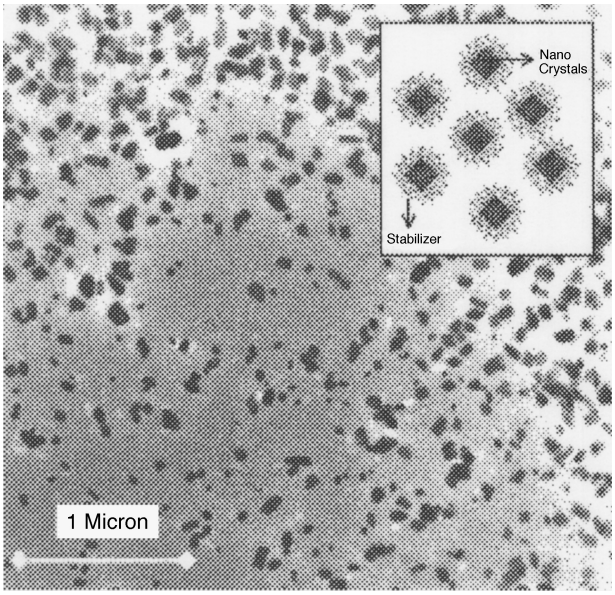

Figure 1. NanoCrystal® drug particle. The transmission electron micrograph of NanoCrystal colloidal dispersion magnified 35,000×. Reprinted from an earlier publication (Ref. [9]) with permission from Elsevier.

than 400 nm and are physically stabilized with a polymeric excipient.[2,9] A physically stable nanosuspension is obtained when the weight ratio of drug to stabilizer was 20:1 to 2:1.[9] Liversidge et al. reported that the poorly water soluble drug, naproxen, was reduced in average particle size from 20–30 μm to 270 nm over 5 days of wet milling. Polyvinylpyrrolidone (PVP) K-15 was used as a stabilizer in the suspension and the ratio between naproxen and PVP K-15 in the nanosuspension was 5:3. The naproxen nanosuspension did not aggregate and remained physically and chemically stable for up to 4 weeks at 4°C.[29,31] In another study, the nanosuspension containing 2% paclitaxel and 1% pluronic F127 was prepared by wet milling for 7 days and had average particle size of about 280 nm. It was found that the higher molecular weight polymeric stabilizer was optimal for effective particle size reduction and shelf stability.[9,30,31]

NanoCrystals particles can be used for oral delivery. In the study of preparaing a nanosuspension of naproxen, the bioavailability of NanoCrystals naproxen was compared to that of the marketed products Naprosyn® (suspension) and Anaprox® (tablet).[9,30] The time to reach maximal drug concentrations in the plasma was approximately 50% less for the NanoCrystals dispersion, while maintaining a 2.5–4.5-fold increase in the area under the curves (AUCs) during the first hour of the study.[9,30] NanoCrystals suspensions are also a suitable dosage form for poorly water soluble injectable products. The nanoparticles produced by the wet milling process provided a significantly higher level dosing than using a traditional approach. Harsh solvents or cosolvents used in the conventional formulations of poorly water soluble drugs are dose limiting due to the toxicity of solvent or excipients.[9] In the comparison of the performance of paclitaxel in the marketed product (Taxol®) using Cremophor EL/ethanol mixture and NanoCrystals nanosuspension, the maximum tolerated dose of the nanoparticle paclitaxel formulation was greater than that of the commercial product. This advantage could improve the delivery efficacy of the poorly water soluble drugs.[9,27,32]

A limitation of the wet milling process that has been reported is the contamination of the product by grinding material.[21] During the wet milling process, erosion of grinding materials occurs and leads to contamination of the product with the grinding media, which are insoluble in the fluid of the GI tract. In addition, wet milling is a batch process. There is batch-to-batch variations detected in the quality of the dispersion, processing time, degree of drug crystallinity, and particle size distribution. These variations affect drug particle stability, powder flow properties, and the efficiency of the delivery system. Milling over a few days also brings the risk of microbiological problems, especially when performing the milling at 30°C or having dispersion media providing nutrition to bacteria.

High Pressure Homogenization

High pressure homogenization is another mechanical process used to prepare suspensions of nanometer-sized particles of poorly water soluble drugs. The formation of nanosuspensions is based on the cavitation forces created in high pressure homogenizers such as the piston-gap homogenizer.[21] In the process, the poorly water soluble drug is first dispersed in an aqueous surfactant solution by high speed stirring, and the suspension is then passed through a high pressure homogenizer applying a typical pressure of 1500 bar and three to 20 homogenization cycles.[21] The suspension passes through a very small homogenization gap in the homogenizer, typically having a width of 25 μm at 1500 bar. Due to the narrowness of the gap, the streaming velocity of the suspension and the dynamic fluid pressure increase. In addition, the static pressure on the fluid decreases below the boiling point of water at room temperature. In consequence, water starts boiling at room temperature and gas bubbles are formed that implode (cavitation) when the fluid leaves

the homogenization gap.[21] These cavitation forces are strong enough to break the drug microparticles into drug nanoparticles.[21,28]

Nanosuspension particles have an average particle size ranging from 40 nm to 500 nm, the proportion of particles larger than 5 μm in the total population being less than 0.1%.[21,28] Figure 2 shows a transmission electron micrograph of an atovaquone nanosuspension particle produced by high pressure homogenization, which has a mean particle size of 468 nm. The particle size of the nanosuspension depends on the hardness of the drug substance, processing pressure, and number of cycles applied. For the poorly water soluble drug, budesonide, a pressure of 1500 bar and 10 cycles led to a mean diameter of 511 nm, increasing the cycle numbers to 15 reduced the size to 462 nm, and increasing the pressure to 2500 bar and 10 cycles led to particles with a mean diameter of 363 nm.[15,21,28] The particle size of poorly water soluble drugs can be produced in a controlled way by adjusting the production pressure and number of cycles.

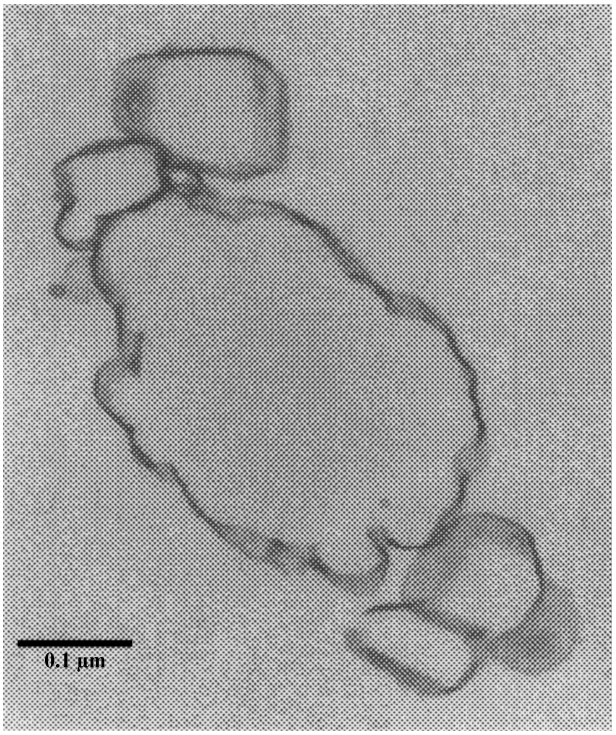

Figure 2. Transmission electron micrographs of an atovaquone nanosuspension by high pressure homogenization process (medium size: 468 nm). Reprinted from an earlier publication (Ref. [21]) with permission from Elsevier.

Stabilization of nanosuspensions against aggregation and coalescence is a primary challenge. The stability of nanosuspensions can be determined by the zeta potential. For a physically stable nanosuspension solely stabilized by electrostatic repulsion, a zeta potential of ±30 mV is required as a minimum.[21,28] In addition, Ostwald ripening is also used to determine the stability of highly dispersed systems.[21] The absence of Ostwald ripening indicates long-term physical stability of an aqueous suspension.[33] It was observed that there was no Ostwald ripening in the nanosuspensions produced by the high pressure homogenization process. This was attributed to the uniform particle size created by the homogenization process.[21,28] The concentration differences in the nanosuspension system were sufficiently low to avoid the ripening effect.

Large-scale production of a drug delivery system is an essential prerequisite for the introduction into the pharmaceutical market of current nanoparticle engineering processes. High pressure homogenizers are available with different capacities from a few hundred to a few thousand liters per hour.[21,28] In addition, instead of passing a few times through one homogenizer, several homogenizers can be placed in series to produce the product in a continuous mode. There are also homogenizers used on a laboratory scale, which can have a batch volume of 20–40 mL, thus allowing the cost-effective processing of expensive drug materials or small amounts of experimental compounds.

Changes in drug crystallinity have been reported for the high pressure homogenization process. A fraction of poorly water soluble drugs in the particles was amorphous in some cases, while the drugs were found to be completely amorphous in other cases.[21] The disadvantage of high pressure homogenization process is that the high pressures used can cause changes in the crystal structure, and as a result, the amorphous fraction in the particle increases in some cases. The batch to batch variation in crystallinity level might be an issue for quantity control. The stability of partially amorphous nanosuspensions will also present a challenge in pharmaceutical industry applications.

Supercritical Fluid Process

Since high energy milling and long processing times can lead to contamination, batch variation, downstream processing difficulties, and compromised stability, a single-step supercritical fluid process would be an excellent alternative, where microparticles and nanoparticles can be formed directly from drug solutions.

Two processes that use supercritical fluids for particle formation have been developed to improve the solubility and dissolution of poorly water soluble drugs.[4] They include rapid expansion of supercritical solutions (RESS) and precipitation with a compressed antisolvent (PCA), which is also referred to as the supercritical antisolvent (SAS) method or the solution enhanced dispersion by the supercritical fluids (SEDS) process.

Precipitation with Compressed Fluid Antisolvent (PCA)

The PCA/SAS/SEDS technique applies a similar concept to the use of an antisolvent in the solvent-based recrystallization process. In the PCA process, CO_2 is used as an antisolvent.[34] Poorly water soluble drug and/or polymer solutions are atomized into a chamber containing compressed CO_2. As the two liquids collide, intense atomization into micronized droplets occurs. Because the solvent(s) must be miscible with the compressed fluid CO_2, subsequent drying of the microdroplets occurs as the solvent(s) and CO_2 mix. Microparticles and nanoparticles are formed after drug precipitation caused by two way mass transfers: extraction of the organic solvent into CO_2 and CO_2 diffusion into the droplets.[35] The mass transfer is dependent upon atomization efficiency and the dispersing and mixing phenomena between the solution droplet and the compressed fluid CO_2. Thus, to minimize particle agglomeration and to reduce or eliminate drying times, high mass transfer rates are desired.[5,36–40]

High mass transfer rates have been successfully achieved in the SEDS process, which uses a coaxial nozzle design with a mixing chamber.[41] The SEDS process was developed and patented by Hanna and York and owned by University of Bradford. The use of a coaxial nozzle[41] provides a means whereby the drug in the organic solvent solution interacts and mixes with the compressed fluid CO_2 antisolvent in the mixing chamber of the nozzle prior to dispersion, and flows into a particle-formation vessel via a restricted orifice. Such nozzles achieve solution breakup through the impaction of the solution by a relatively higher velocity fluid. The high velocity fluid creates high frictional surface forces, causing the solution to disintegrate into droplets. A wide range of materials have been prepared as microparticles and nanoparticles using the SEDS process,[10] including salmeterol xinafoate (Fig. 3). By controlling and changing the process parameters, salmeterol xinafoate products composed of particles with different particle sizes and particle shapes were produced. The mean particle size of salmeterol xinafoate particles ranged from 1 μm to 20 μm.[41] It was reported that salmeterol xinafoate particles obtained at 50°C had a blade-like shape with reduced elongation compared with the acicular, needle-shaped particles produced at 60°C.[41] By processing in different regions of the supercritical phase with the same organic solvent, two salmeterol xinafoate polymorphs have been prepared by the SEDS process. Samples of the two polymorphs exhibited physicochemical stability and no measurable interconversion after 5 years. In another study, a new polymorph of fluticasone propionate has been produced by the same process, which also enabled control over the particle size and shape of formed particles. The new polymorph of fluticasone propionate exhibited improved drug delivery characteristics in a metered dose inhaler (MDI) formulation compared with conventionally crystallized and micronized drug.[42]

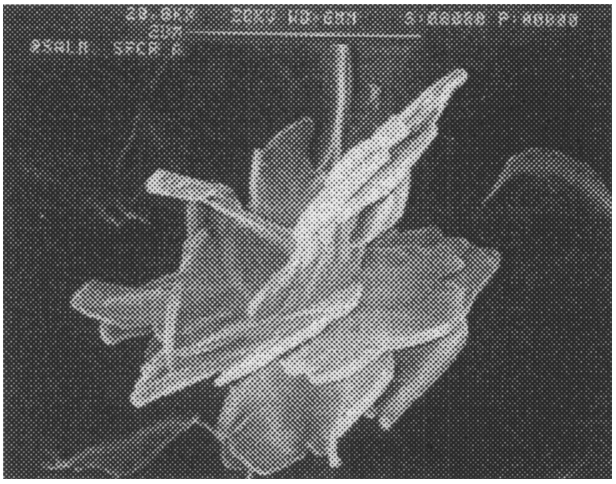

Figure 3. SEM microphotograph of solution enhanced dispersion by supercritical fluids (SEDS)-processed salmeterol xinafoate. Reprinted from an earlier publication (Ref. [10]) with permission from Elsevier.

Subramaniam et al. developed a process that involved deliberate generation of high energy sonic waves that was substantially independent of any impaction and frictional forces typical of nozzles used in PCA process. The process was patented[43] by The University of Kansas. The sonic waves are generated in the energizing gas stream or in the dispersion itself. The ultrasonic nozzle-based process is capable of producing discrete nanoparticles in a narrow size range. As discussed above, a key step in the formation of nanoparticles is to enhance the mass transfer rate

between the droplets and the antisolvent before the droplets coalesce to form bigger droplets.[16,43] With the ultrasonic nozzle, the sound waves assist the antisolvent's breakup into small droplets, increasing the interfacial area. The turbulence created by the focused sound waves enhances the mass transfer rate between the droplets and the CO_2.[16,43] A significant decrease in the average particle size is achieved with the use of the ultrasonic nozzle-based SAS process. In the study, it was reported that the hydrocortisone particles produced by the ultrasonic nozzle-based SAS process were discrete, nearly spherical, and appeared to be narrowly distributed around 500 nm. In contrast, 1 μm wide and nearly 1 mm long fibers were produced by using the conventional SAS process with the 100 μm capillary nozzle.[43] Sound waves, rather than inertial or frictional forces, are exploited for droplet formation. Hence, the diameter of the line into which the spray solution is introduced can be larger than that of either the capillary or micro-orifice nozzles. This larger diameter allows for higher solution throughput and reduces the probability of nozzle plugging, dramatically increasing manufacturing efficiency.

Rapid Expansion from Liquefied-Gas Solution and Homogenization

Johnston et al. developed a process based on supercritical fluid, rapid expansion from supercritical to aqueous solution (RESAS), which produced stable nanosuspensions of poorly water soluble drugs.[44–46] The principle of this process is to induce rapid nucleation of the supercritical fluid dissolved drugs in the presence of surface modifying agents resulting in particle formation with a desirable size distribution in a very short time.[6] Phospholipids or other suitable surfactants are integrated into the process as a solution or dispersion in the supercritical fluid.[6,47] The surface modifying agents serve to stabilize the newly formed small particles and suppress any tendency of particle agglomeration or particle growth while they are being formed.[47] While very rapid precipitation is a characteristic of precipitation of solutes from supercritical fluids, the rapid intimate contact with the surface modifier is achieved by having the surface modifiers dissolved in the supercritical fluid containing the dissolved drug.[47] A rapid intimate contact between the surface modifier and the newly formed particle substantially inhibits the crystal growth of the newly formed particle.

The RESAS process successfully incorporates aqueous stabilizing solutions into the RESS process to trap 500 nm particles of poorly water soluble drugs.[45] In RESAS, the surfactant diffuses rapidly to the particle surface to impede particle agglomeration and growth. Young et al. reported that cyclosporine nanoparticles were formed by spraying a solution (in CO_2) into a Tween-80 solution to prevent nanoparticle flocculation and agglomeration. Cyclosporine particles formed by RESAS had a size of 500–700 nm and could be stabilized for drug concentrations as high as 6.2 and 37.5 mg/mL in 1.0% and 5.0% (w/w) Tween-80 solutions, respectively (Table 1).[45] At a drug/surfactant ratio above 0.6–0.7 the surfactant can no longer stabilize the particles, resulting in broader size distributions.[45] The RESAS process produced smaller particle sizes of organic and inorganic water-insoluble drugs than in the case of RESS into air.[45]

Table 1. Cyclosporine microparticles prepared by RESAS of a 1.0% (w/w) solution into 20.0 mL of 5.0% (w/w) Tween-80 aqueous solution.[a]

Expt no.	Solution flowrate (mL/min)	Spray time (min)	Drug concn. (mg/mL)	Yield (%)	Particle size (nm)	Drug/surfactant ratio
8	1.25	8	3.97	82	15–560	0.075
9	0.57	19	5.55	95	340–500	0.105
10	0.55	19	5.58	99	490–600	0.106
11	0.56	20	6.10	96	410–520	0.116
12	0.24[b]	112	23.8	64	410–545	0.452
13	0.55	70	37.5	100	500–660	0.713
14	0.37[b]	122	45.9	64	380–550 970–1550[c]	0.873

[a]T_{soln}=30.0° C, $T_{preheater}$=60.0° C, ΔP=345 bar.
[b]10.0 mL receiving solution.
[c]Two peaks: 37% in lower peak by intensity averaging. 63% in lower peak by weight averaging.
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Pace et al. combined RESAS with high pressure homogenization to provide a stable and high payload drug delivery system.[6,47] The microparticle or nanoparticle suspensions were formed by rapid expansion into an aqueous medium of a compressed solution of the compound and surface modifiers in a liquefied gas and homogenizing the aqueous suspension thus formed with a high pressure homogenizer [Rapid Expansion of Liquefied-Gas Solution and Homogenization (RELGS-H)].[6,47] RTP Pharmaceuticals Inc. patented this process and included it in the Insoluble Drug Delivery (IDD) technology, which was later licensed to Baxter Healthcare Corporation and incorporated into NANOEDGE technology. In this process,[6] a poorly water soluble drug and a surface modifier are first dissolved in a liquefied compressed gas solvent. A range of compressed gases in the supercritical or subcritical fluid includes but is not limited to gaseous oxides such as carbon dioxide and nitrous oxide; alkanes; alkenes, alcohols, and isopropanol; ketones; ethers; esters; halogenated compounds, etc.[47] The compressed fluid solution is then expanded into an aqueous solution containing a second surface modifier and water-soluble agents, thereby producing a suspension.[47] Finally, the suspension is homogenized into nanosuspensions.[47] The high pressure homogenization could enhance the surface modifier interaction with the surface of micronized particle.[47] The process produces surface modified particles in a range of 5 to 100 nm in size. The particle size of nanosuspensions is controlled by parameters of the rapid expansion and homogenization processes. For example, a solution containing Fenofibrate (2 g), Lipoid E-80 (0.2 g), and Tween-80 (0.2 g) in liquefied carbon dioxide pressurized to 3000 PSI was expanded through a 50-mm orifice plate into water held at atmospheric pressure and room temperature (22°C).[47] A fine suspension of fenofibrate was obtained with a mean particle size of about 200 nm. The process provides drug payloads up to 200 mg/mL. The ratio between the drug and lipid was reported as high as 5:1 (w/w) in the formulation of poorly water soluble drug, itraconazole.[6,47] As is well known, there are very serious destabilizing problems of nanosuspensions such as aggregation and sedimentation due to physical force. This process circumvents these problems. It was reported that formulations of propofol showed stability at storage temperatures between 2–8° C and 40° C over a period of more than 1 year.

The success of the above supercritical fluid techniques depends heavily, however, on the efficiency of atomization of the solution into the supercritical fluid. The formation of a particle containing a poorly water soluble drug and a water soluble excipient is limited by the lack of solvent systems that will dissolve both hydrophilic and hydrophobic substances. The low solubility of most poorly water soluble drugs and surfactants in supercritical CO_2 results in low production rates of powders. The typical approach to enhance drug loading in CO_2 is to increase the process temperature, but the elevated temperature may accelerate degradation of drugs. Another limitation is the high pressure required for these processes. Such operating pressures are not commonly used in the pharmaceutical industry.

Cryogenic Spray Processes

The cryogenic spray process is an attractive alternative to form microparticles and nanoparticles of poorly water soluble drugs. Both halocarbon refrigerants and liquid nitrogen have been used as cryogenic media in conventional spray-freezing into vapor processes.[48–59] In these procedures, the feed solution is atomized through a nozzle positioned at a distance above the boiling refrigerant. The droplets gradually solidify while passing through the cold halocarbon vapor, and freeze completely as contact is made with the boiling refrigerant liquid. Gombotz et al. and Gusman and Johnson have developed spray-freezing into nitrogen vapor processes for the purpose of using an inert cryogen to capture frozen drug particles following atomization.[60–63] Because atomization occurs into the nitrogen vapor above the liquid gas, the solution droplets gradually agglomerate and solidify while passing through the vapor phase and then settle onto the surface of the cryogenic liquid.[5] As a result of droplet agglomeration, broad particle size distributions and nonmicronized dry powders may result.

Spray Freezing into Liquid Process

Recently, a new cryogenic spray process, spray freezing into liquid (SFL) process was developed to overcome such problems and this process was patented by The University of Texas at Austin in 2001[64] and commercialized by The Dow Chemical Company. The SFL process is a cryogenic atomization process in which an aqueous, organic, or aqueous-organic cosolvent solution, aqueous-organic emulsion, or suspension containing a drug and pharmaceutical excipient(s) is atomized directly into a compressed liquid, such as compressed fluid CO_2, helium, propane, ethane, or the cryogenic liquids including nitrogen, argon, or hydrofluoroethers.[64] The SFL process utilizes the atomization of a feed solution containing drugs and/or excipient(s) directly into a cryogenic liquid to produce

frozen nanostructured particles. The frozen particles are then lyophilized to obtain dry, free-flowing micronized powders. The advantages of the SFL process result from intense atomization and rapid freezing rates. Because liquid–liquid impingement occurs between the pressurized feed solution exiting the nozzle and the cryogenic liquid, a high degree of atomization is achieved by spraying directly into the cryogenic liquid as opposed to spraying into the vapor phase above the cryogenic liquid. Ultra-rapid freezing rates are achieved because of the low temperature of liquid nitrogen and the formation of high-surface area droplets. The ultra-rapid freezing rates prevent the phase separation of solutes within the feed solution and induce formation of amorphous structures. The high degree of atomization and ultra-rapid freezing rates led to amorphous nanostructured particles with high surface areas, enhanced wetting, and significantly enhanced dissolution rates.[35,65–71]

Hu, Johnston, and Williams reported that the SFL process may use organic solvents such as acetonitrile, as the solution source solvent in addition to solution containing water or water/organic cosolvent such as the water tetrahydrofuran (THF) cosolvent system.[65] The SFL powders from the organic system and the aqueous-organic cosolvent system exhibited similar and significantly enhanced dissolution rates compared to the micronized bulk drugs. The SFL acetonitrile system offers several advantages, including increasing the drug loading in the SFL feed solution and decreasing the drying time for lyophilization following the SFL process. All of these attributes have a positive effect on the scale-up of the SFL process in the product manufacture.

A recent study also demonstrated that rapidly dissolving SFL micronized powders with high potency (up to 91%) have been produced by SFL with an organic solvent mixture.[66] The high potency SFL powders contained amorphous nanostructured aggregates with high surface area and excellent wettability. For example, SEM micrographs of the SFL danazol/PVP K-15 with 50% potency revealed (Fig. 4A) small porous aggregates with an average geometric diameter of about 1.5 μm. Higher magnification showed that the aggregate was also composed of many smooth primary nanoparticles with a geometric diameter of about 100 nm (Fig. 4B). In only 2 minutes, 99% of the danazol dissolved in sodium lauryl sulfate (SLS)/Tris dissolution media from the SFL danazol/PVP K-15 powders. The composition of surfactant in the product could be controlled simply by the feed composition, as all of the surfactant precipitated with the drug. In SFL, solvent mixtures may be formulated to achieve high drug solubility in order to produce high potency powders. Rogers et al. reported that highly concentrated emulsions could also be processed by SFL.[70] The large quantities of poorly water soluble drugs and excipients could be processed with lower quantities of solvents when emulsion formulations were SFL processed. The SFL-micronized powders from emulsions wetted and dissolved as fast as the SFL-micronized powders from solutions.

The SFL-processed frozen powders can be dried by lyophilization or the atmospheric freeze-drying (ATMFD) technique, which uses cryogenic air to fluidize the powder and facilitates mass transfer rates in solvent sublimation.[69] The ATMFD technique is a scalable freeze-drying process that does not require the use of a vacuum to sublime solvents. Thus, scalability issues due to vacuum limitation in lyophilization are eliminated with ATMFD. Therefore, large micronized SFL powder batches can be produced. The engineered SFL-micronized powders can be used for different delivery systems. If the dissolution enhancement of poorly water soluble drug is desired, the poorly water

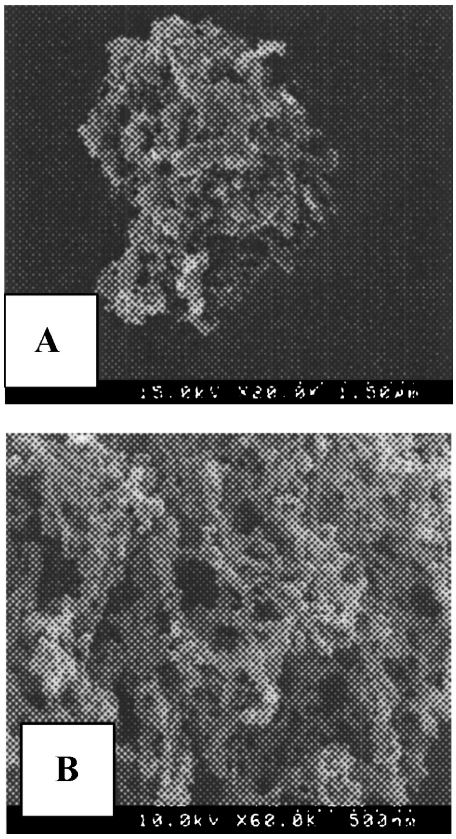

Figure 4. SEM micrographs of SFL danazol/PVP K-15 nanoparticles.

soluble drug could be engineered within an excipient matrix for immediate release.

The SFL-micronized powders can also be used for respiratory delivery. The SFL-micronized powders have been compressed into a tablet for oral delivery. The SFL process offers a highly effective approach to produce high potency nanoparticles contained in larger structured aggregates with rapid dissolution rates for poorly water soluble drugs. The ability to stabilize nanostructured high surface area drug powders in high glass transition temperature (T_g) formulations and to maintain rapid dissolution rate of SFL-micronized powders in the tablet formulation offers great promise for pharmaceutical development and manufacturing to improve dissolution rates of poorly water soluble drugs.

Solvent Evaporation Process-Evaporative Precipitation into Aqueous Solution Process

Another new nanoparticle formation process, evaporative precipitation into aqueous solution (EPAS) was developed and patented by The University of Texas at Austin and licensed to The Dow Chemical Company in 2001.

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of poorly water soluble drugs. The drug is first dissolved in a low boiling liquid organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's normal boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. A stabilizing surfactant is added to the organic solution, the aqueous solution, or both to optimize particle formation and stabilization. The nozzle is immersed into the aqueous solution to ensure that the nucleating drug particles contact the hydrophilic stabilizing surfactant rapidly, inhibiting crystallization and growth of the drug particles. The stable aqueous drug suspension is dried by a variety of techniques, including ultra rapid freezing in conjunction with lyophilization, or spray drying. The stabilization of the drug particles with water soluble stabilizers in the aqueous suspensions facilitates dissolution rates of the final powder after drying. The EPAS process offers several advantages vs. the spray-drying process. The rapid evaporation of the heated organic solution in EPAS results in fast nucleation leading to amorphous nanoparticle suspensions. A variety of hydrophilic stabilizers were found to diffuse to the surface of the growing particles rapidly enough to prevent growth of the nanoparticles. Johnston's lab has produced nanoparticle suspensions of cyclosporine A[72] with a particle size ranging from 130 nm to 460 nm using the EPAS process (Table 2).

The EPAS process produces surfactant-stabilized aqueous suspensions that are dried to form micronized powder with rapid dissolution rates. Sarkari et al.

Table 2. EPAS results for 10% (w/w) phosphatidylcholine in the aqueous solution.

C_{soln} (% w/v)	D_{avg} (nm)	Particle size distribution (nm)	$C_{aq.}$ (mg/mL)	Yield (%)	Drug surfactants ratio (w/w)
0	131	53–66 (65%); 225–323 (35%)	0		0
1	253	134–160 (48%); 324–386 (52%)	14.4	96	0.14
2	526	120–212 (13%); 375–663 (87%)	30.8	87	0.30
5	477	217–253 (20%); 507–615 (80%)	37.1	100	0.37
5	408	96–166 (19%); 287–496 (79%)	34.6	98	0.35
5	446	53–73 (44%); 188–414 (39%); 1252–2357 (17%)	31.8	90	0.32
36.0a	460	123–642 (97%)	35.2	83	0.35
36.0a	466	267–327 (61%); 653–801 (39%)	34.9	79	0.35

[a]Phosphatidylcholine in organic solution.
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reported that the dissolution rates of PVP K15 stabilized powders produced by EPAS are much faster than those previously produced by solvent evaporation without an aqueous phase.[72,73] In EPAS, the surfactant migrates to the drug–water interface during particle formation, and the hydrophilic segment is oriented outwards towards the aqueous continuous phase. In the spray-drying process, which does not use water, this driving force for forming a hydrophilic coating on the particle is not present. In EPAS, the rapid nucleation of the drug followed by adsorption of surfactant at the drug-aqueous solution interface leads to colloidal suspensions of micron-sized drug particles coated by a hydrophilic stabilizer. The stabilizer inhibits crystallization of the growing particles.[72] After drying to form a powder, a hydrophilic surface is available on the drug particle surface to facilitate rapid dissolution rates, which could be achieved with a variety of ionic and nonionic low molar mass and polymeric stabilizers present originally in the organic phase, aqueous phase, or both. Hydrogen bonding and/or hydrophobic interactions between poorly water soluble drugs and stabilizers provide intimate contact and much higher dissolution rates than obtained from a simple physical mixture of the two.

Chen, Williams, and Johnston reported that high dissolution rates were obtained for danazol produced by EPAS with PVP 40T, PVP K-15, or PVP 40T together with SLS as stabilizers.[74] The high dissolution rates, about 90% in 2 minutes with a drug/surfactant ratio of 9:1, were remarkable given the high potencies and very low amounts of excipients. Since only about 5% of the surfactant required for forming suspensions was adsorbed onto the particles, the rest was removed after centrifugation. After removal of the free surfactant and drying, the particles were redispersed in pure water without any growth in particle size or loss in surface area. The dissolution rates were high only for surfactants with an adsorption of 10% (w/w) or more during the EPAS spray.[74] The high surfactant adsorption levels were required to prevent particle agglomeration and growth. These results indicate that the small particle size and large surface area of the surfactant-coated particles, with reduction in crystallinity less than 20%, was enough to produce high dissolution rates. The EPAS suspensions may be used in parenteral formulations to enhance bioavailability or may be dried to produce solid oral dosage forms. The ability to engineer stable particles with high potencies and high dissolution rates with EPAS presents new opportunities in the development of commercial formulations for poorly water soluble drugs.

In summary, recent advances in commercially or potentially commercially available nanoparticle engineering processes have been discussed. These nanoparticle engineering processes, including wet milling, high pressure homogenization, PCA/SEDS/SAS, RESAS/RELGS/RELGS-H, SFL, and EPAS techniques, have successfully incorporated poorly water soluble drugs alone, or with excipients into the microparticles or nanoparticles with significantly improved in vitro dissolution rate and in vivo bioavailability. As the percentage of poorly water soluble experimental compounds is increasing, nanoparticle engineering processes for enhancement of dissolution rates of poorly water soluble drugs offer great promise for pharmaceutical development and manufacturing to bring these experimental compounds into the market.

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