Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report

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ABSTRACT

The purpose of this report was to compile relevant technical information on various alternative strategies that can be used as feasible approaches in the development of solid dispersions. The technologies discussed in the report are spray coating on sugar beads with a fluidized bed coating system, hot melt extrusion, direct capsule filling, electrostatic spinning, surface active carriers, and supercritical fluid technology. The focus is on basic principles, the equipment involved, and the relevant scale-up work. These technologies have been found to eliminate several drawbacks posed by the conventional methods of manufacturing of solid dispersions such as laborious preparation methods, reproducibility, scaling up of manufacturing processes, stability of drug, and vehicle.

KEYWORDS: hot-melt extrusion, solid dispersions, direct capsule filling, electrostatic spinning, surface-active carriers, supercritical fluid technology.

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INTRODUCTION

The progress in treatment of diseases has been evident with an upsurge in development of new drugs. An estimated 40% of these drugs are poorly water soluble. Although most of the drugs have encouraging experimental data obtained in vitro, the in vivo results have been disappointing. The attributes include

1. poor absorption, rapid degradation, and lamination (peptides and protein) resulting in insufficient concentration,
2. drug distribution to other tissues with high drug toxicities (anticancer drugs),
3. poor solubility of drugs, and
4. fluctuations in plasma levels owing to unpredictable bioavailability.

The enhancement of oral bioavailability of such poorly water-soluble drugs remains one of the most challenging aspects of drug development.

The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by cosolvents, and particle size reduction.[1] Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion.[2,3] When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. In spite of these advantages, only 2 products have been marketed since the development of this technology 4 decades ago. The limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include

1. laborious and expensive methods of preparation,
2. reproducibility of physicochemical characteristics,
3. difficulty in incorporating into formulation of dosage forms,
4. scale-up of manufacturing process, and
5. stability of the drug and vehicle.

Various methods have been tried recently to overcome the limitations and make the preparation more practically feasible

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while, at the same time, retaining both the physicochemical and bioavailability enhancing properties of solid dispersions. Some of the suggested approaches to overcome the aforementioned problems and lead to industrial scale production are reviewed in the Alternative Strategies section.

ALTERNATIVE STRATEGIES

Spraying on Sugar Beads Using a Fluidized Bed Coating System

The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granules ready for tableting or drug-coated pellets for encapsulation in one step. The method has been applied for both controlled- and immediate-release solid dispersions.[4,5]

Itraconazole (Sporanox oral capsules, Janssen Pharmaceutica, Titusville, NJ) coated on sugar sphere, is made by layering onto sugar beads a solution of drug and hydroxypropylmethylcellulose (HPMC) in an organic solvent of dichloromethane and ethanol.[6] A solid solution of drug in HPMC is produced upon coating (cosolvent evaporation) and controlled drying of coated beads in a closed Wurster process. As this thin film dissolves in water or gastric fluid, the molecularly dispersed itraconazole is released at supersaturated concentration. HPMC acts as a stabilizer to inhibit recrystallization of the itraconazole. The supersaturated solutions of itraconazole are sufficiently stable to allow for absorption and distribution.

Modifications to the above method, wherein the use of organic solvents is avoided, have been reported. These alterations involve the use of hot-melt fluid bed technique, where nonpareils are coated with polyethylene glycols (PEGs) having molecular weights between 11 450 and 4600.[7]

Hot-melt Extrusion

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971.[8] Since the turn of the century, many studies have been conducted on this process for the preparation of solid dispersion. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient.[9] The process has been useful in the preparation of solid dispersions in a single step. Hot-melt extrusion method is used in the preparation of various dosage forms in the pharmaceutical industry such as preparation of sustained-release pellets. (An extruder consists of 2 distinct parts: a conveyer system that transports the material and sometimes imparts a degree of distributive mixing; and a dye system that forms the materials into the required shape [Figure 1].)

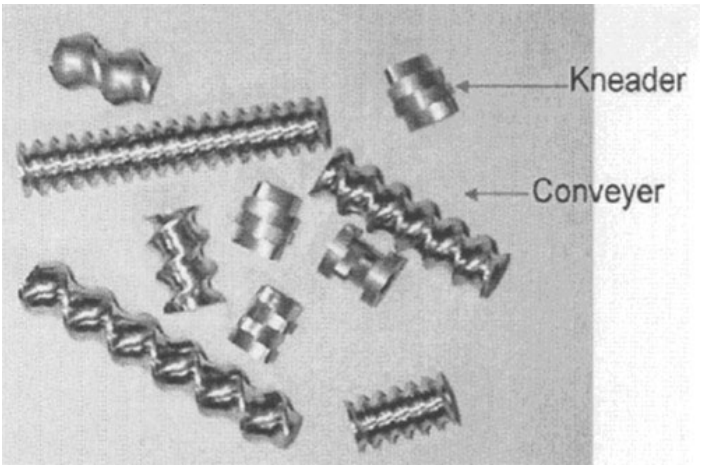

Figure 1. Screw and kneading element. Reproduced with permission from Zia H et al.[10]

The drug carrier mix is filled in the hopper and is conveyed, mixed, and melted by the extruder (Figure 2). The die then shapes the melt in the required form such as granules, pellets, films, or powder that can be further processed into conventional tablets or capsules. The advantages of hot-melt extrusion include lower temperature and shorter residence time of the drug carrier mix (<2 minutes), absence of organic solvents, continuous operation possibility, minimum product wastage, good control of operating parameters, and possibility to scale up. Oxygen and moisture may be excluded almost completely for substances prone to oxidation and hydrolysis. The disadvantages are few and mainly relate to negative effects of shear force.

A fast-release dosage form of carbamazapine was prepared using lactose as a hydrophilic filler and PEG 4000 as a binder at a temperature below its melting point.[11] Solubility and the dissolution rates of 17 β-estardiol hemihydrate was improved using PEG 6000, polyvinylpyrrolidone (PVP), or a vinylpyrrolidone/vinyl acetate-copolymer and Sucroester WE15 or Gelucire 44/14 employing this process.[12] Highly enhanced dissolution rate from extruded powder containing 10% 17 β-estardiol hemihydrate 50% PVP and 40% Gelucire 44/14 was preserved when processed into tablets and met the United States Pharmacopeia (USP) XXIII requirements. Solid dispersions prepared by hot-melt extrusion have been used for clinical testing. Melt-extruded ibuprofen dispersions were compared with the ibuprofen lysinate in healthy volunteers. Bioequivalence was demonstrated with the relevant parameters area under the curve (AUC) and maximum concentration (C_{max}). Also, the t_{max} as a measure for onset proved to be equivalent, with 0.5 hours for test and reference.[13]

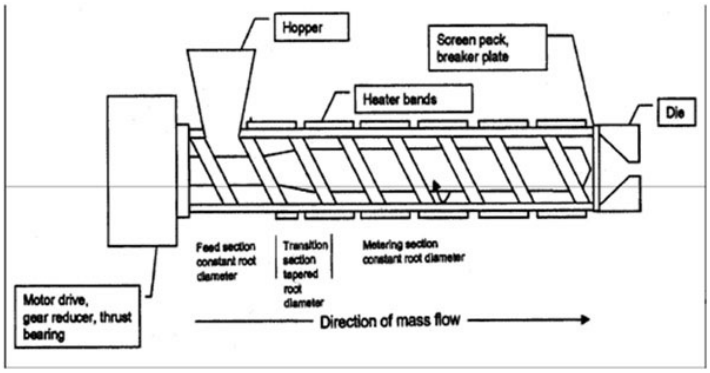

Figure 2. Composition of single-screw extruder. Reproduced with permission from Zia H et al.[10]

An amorphous solid dispersion of Itraconzole/HPMC (40/60 wt/wt) was formed from milled melt extrudate and resulted in a significantly increased dissolution rate compared with the physical mixture; the formulation was found chemically and physically stable for periods in excess of 6 months.[14,15] The tablets formed by compressing milled melt-extruded glassy powder with additional excipients showed high oral bioavailability.[16]

Direct Capsule Filling

The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978.[17] It was not until much later that the potential application of the technique for solid dispersions was fully realized. Laboratory-scale semiautomatic equipment[18] and large-scale manufacturing equipment for direct capsule filling are commercially available. Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. The filling of hard gelatin capsules has been feasible in molten dispersions of triamterene-PEG 1500 using a Zanasi LZ 64 capsule-filling machine (Zanasi Co, Bologna, Italy).[19] This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross-contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug.[20] A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (eg, polysorbate 80 with PEG, phosphatidylcholine with PEG).[21,22] The temperature of the molten solution should not exceed ~70°C because it might compromise the hard-gelatin capsule shell.

Electrostatic Spinning Method

The electrostatic spinning method technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology.[23,24] This technology is now applied in the pharmaceutical field.[25,26]

In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength.[27]

Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and nonbiodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct incorporation of the materials into a capsule. Itraconazole/HPMC nanofibers have been prepared using this technique.[28] Electrospun samples dissolved completely over time, with the rate of dissolution being dependent on the type of formulation presentation and the drug:polymer ratio. Because the technique has been successfully used in other fields, the technique can be extended in the pharmaceutical industry for the preparation of solid dispersions.

Surface-active Carriers

A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs. The surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs have been of great interest in recent years.

Two of the important surface-active carriers are Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Gelucire 44/14 (Gattefosse´ Corp, Gennevilliers, France) has commonly been used in solid dispersion for the bioavailability enhancement of drugs.[20,21,29-34] Gelucire 44/14 is a mixture of glyceryl and PEG 1500 esters of long-chain fatty acids and is official in the European Pharmacopoeia as lauryl macrogolglycerides; the suffixes 44 and 14 in its name refer, respectively, to its melting point and hydrophilic-lipophilic balance (HLB) value. Vitamin E TPGS National Formulary (NF) (Eastman, Kingsport, TN) is prepared by the esterification of the acid group of *d*-R-tocopheryl acid succinate by PEG 1000. The material has an HLB value of 13 and is miscible with water in all parts. Its melting point, however, is relatively low (38°C), and it may require mixing with other carriers to increase melting temperatures of formulations.

A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-active carrier.[21,35] Polysorbate 80 is liquid at room temperature; it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure. As much as 75% (wt/wt) Polysorbate 80 was incorporated, PEG remained semisolid, and the lowering of the melting temperature of the PEG used was <12°C.[35] The PEG-polysorbate carriers have been found to enhance dissolution[36] and bioavailability[32] of drugs from the solid dispersions. Incorporation of 5% (wt/wt) phosphatidylcholine resulted in enhanced dissolution rate of nifedipine from a PEG-based solid dispersion.[22] Pulverized solid dispersions in PEG containing varying amounts of ionic and nonionic surfactants, including sodium dodecyl sulfate and Polysorbate 80 gave increased dissolution rate of drug.[37]

A solid dispersion of poorly soluble REV5901 in Gelucire 44/14 under a fasting regimen had much higher bioavailability in human volunteers than that of a tablet formulation even though the micronized form of drug and a wetting agent were used in the tablet.[38] The bioavailability of ubidecarenone in dogs from solid dispersion in Gelucire 44/14 and the Gelucire 44/14-lecithin mixture were 2 and 3 times higher, respectively, than that of commercially available tablet.[30]

One of the limitations of bioavailability enhancement by this method might be the low solubility of drug in available carriers.[31,39] The desired doses of a drug cannot be solubilized and filled into hard-gelatin capsules if adequate solubility in a carrier cannot be obtained. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott Co, Abbott Park, IL) from the market. The crystallization of drug adversely influenced the dissolution of the ritonavir capsule, and the product was switched to a thermodynamically stable solution formulation.

Initial formulation development studies can be conducted by filling hot solutions or dispersions into hard-gelatin capsule shells manually by using pipettes or by using laboratory-scale semiautomatic equipment.[18] Equipment is also available to scale-up the manufacturing process and for large-scale manufacturing.[40] Solutions can also be filled into soft-gelatin capsules for which the solution temperature should remain <40°C.[41] A couple of hard-gelatin[42,43] and a soft-gelatin capsule product, prepared using these techniques involving the use of surface-active carriers, have been marketed in recent years.

Supercritical Fluid Technology

It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. SCF technology offers tremendous potential, as it is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.

In the pharmaceutical field, the SCF technology was industrially applied in the early 1980s; the applications included the purification of surfactants and pharmaceuticals,[44] fractionation of polymeric materials and chemical reactions and polymerizations. In the same period, interest in using SCFs for precipitation and crystallization processes was developing for pharmaceutical materials. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (ie, liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points.[45] Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application.[46] These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications.[45,47]

As described above, carbon dioxide is one of the most commonly used SCFs because of its low critical temperature (Tc = 31.1°C) and pressure (Pc = 73.8 bar). Apart from being nontoxic, nonflammable, and inexpensive, the low critical temperature of CO_2 makes it attractive for processing heat-labile molecules (eg, products of biotechnology). The ability to rapidly vary the solvent (or antisolvent) strength and, thereby, the rate of supersaturation and nucleation of dissolved compounds is exploited as an alternative technology for particle formation under various names that are essentially based on 3 key process concepts:

1. precipitation from supercritical solutions—rapid expansion of supercritical solution (RESS);
2. precipitation from saturated solutions using SCF as an antisolvent—gas antisolvent (GAS), precipitation with compressed antisolvent (PCA), supercritical antisolvent (SAS), aerosol solvent extraction system (ASES), and solution enhanced dispersion by supercritical fluids (SEDS) process; and
3. precipitation from gas-saturated solutions—particles from gas-saturated solutions (PGSS).

SCF technology provides a novel alternative method of generating small particles, with higher surface areas, that are free flowing and very low in residual organic solvent.[48] The formation of small particles is, however, highly dependent

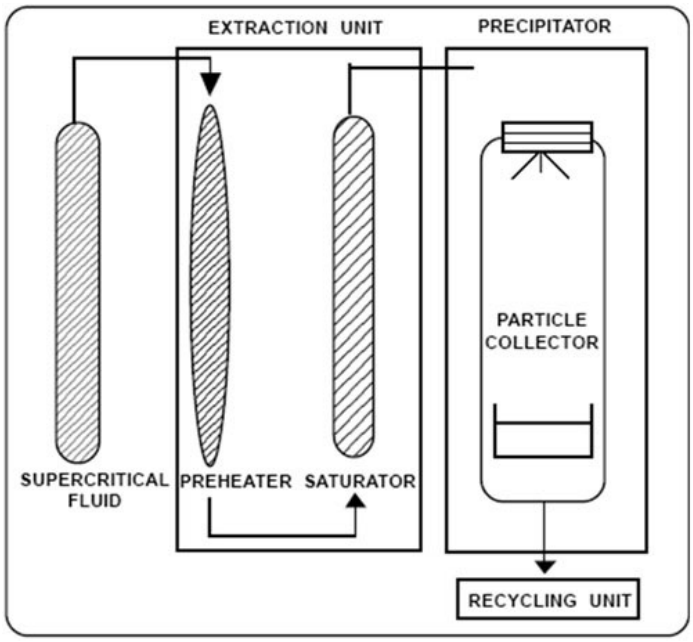

Figure 3. Schematic diagram of precipitation from supercritical solutions—rapid expansion of supercritical solution (RESS). Reproduced with permission from Kakumanu, VK and Bansal, AK.[49]

on the materials in question and requires optimization of processing conditions. These aspects of the technology can be applied to formulate coprecipitates of drug in water-soluble carrier and thus overcome many aforementioned problems of conventional methods (Figure 3). The solid dispersion prepared from this method has been found to increase the dissolution considerably. This technique has also been used to precipitate homogeneous antracene-phenantrene crystals of solid solution.[50] The applicability of RESS for preparation of solid dispersions is limited by the very low or negligible solubility of most drugs and polymers in the commonly used supercritical CO_2.

In the SEDS process,[51] the size of droplets coacervated in a supercritical medium is controlled by the specific nozzle design, the parallel flow of supercritical medium with the solution in coaxial passages, and the mixing of solution and SCF in the nozzle before the outlet end of the nozzle (Figure 4). SEDS process was used to form solid solution particles from a model drug and 2 different types of carriers, Mannitol and Eudragit E 100.[52] One-phase solid solution was obtained when coprocessed with Eudragit E 100 but was not obtained for the mannitol coprecipitate. This result emphasized the role of excipients used in the process. Solid solutions of several drugs have been produced using the SEDS technique with hydroxypropylcellulose, ethylcellulose, and polyvinylpyrrolidone as carriers.[53]

In the PGSS process, a melt of the drug and the carrier saturated with supercritical CO_2 is rapidly cooled by adiabatic expansion of CO_2, whereupon the solid dispersion precipitates in the form of microparticles (Figure 5). This rapid cooling and expansion of CO_2 produces fine particles with a narrow particle size distribution and, thereby, avoids the comminution step. In principle, the technique is similar to the RESS process except that on expansion the phase separation is caused by evaporation of the volatile component from the homogeneous liquid phase. Because no organic solvent is used, the tedious process of removal of residual solvent is completely avoided (CO_2 is an inert gas at atmospheric pressure). This is the advantage over the classic methods of preparation of solid dispersions. The added advantage from an industrial aspect is the recovery of the coprecipitate powder in 1 step. Solid dispersions of nifedipine and felodipine[54] and fenofibrate[55] were prepared with PEG 8000 using the PGSS process. The dissolutions of the drugs were compared with that of micronized drugs. The solid dispersions consistently showed better dissolution rates than the micronized drugs.

The relative low solubilities of pharmaceutical compounds in unmodified CO_2 are exploited in the GAS process, wherein the solute of interest (drug, polymer, or both) is dissolved in a conventional solvent. High solubilities of SCFs in organic solvents cause a volume expansion, decreasing the density and solvent power of organic solvent and leading to precipitation of solute particles.[56] Crystallization of insoluble solute in SCFs from liquid solution using the GAS method was first done in 1989.[57] Its advantages include higher solute throughput and flexibility of solvent choice.

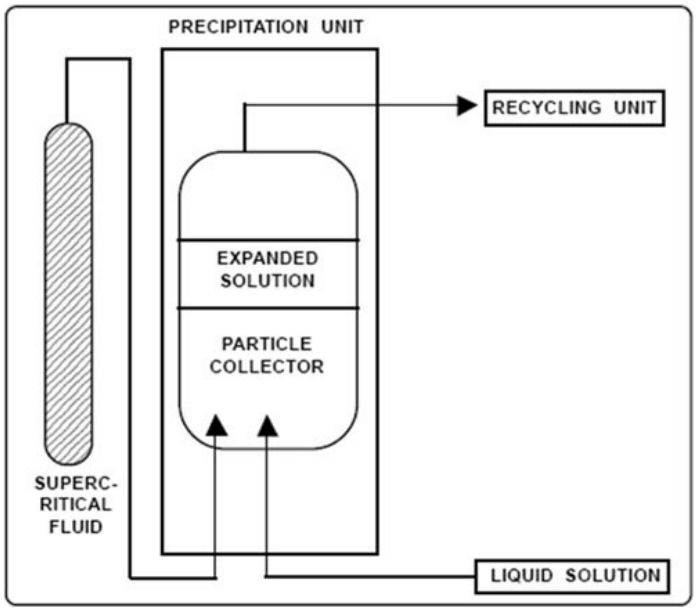

Figure 4. Schematic diagram of precipitation from saturated solutions using supercritical fluid as an anti-solvent—gas anti-solvent (GAS). Reproduced with permission from Bansal AK et al.[49]

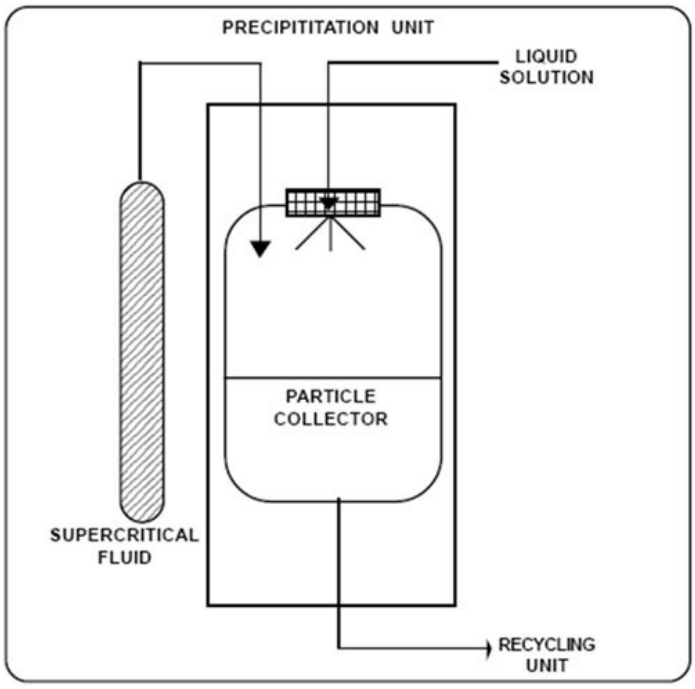

Figure 5. Schematic diagram of precipitation from gas-saturated solutions—particles from gas-saturated solutions (PGSS). Reproduced with permission from Bansal AK et al.[49]

This method was used to prepare carbamazepine solid dispersions with PEG 4000.[58] These solvent-free binary systems showed remarkable dissolution characteristics. The prismatic carbamazepine crystals showed a dramatic change to needle-shaped, light, voluminous powder after treatment with supercritical CO_2, with improved dissolution, reduced particle size, and increased wettability. Carbamazepine solid dispersions in PEG 8000 alone or in combination with Gelucire 44/14 or TPGS formulated by the GAS and conventional solvent evaporation methods described the mechanism of enhanced bioavailability of carbamazepine.[59] The bioavailability of carbamazepine was more a function of dissolution than the membrane effects. The GAS method rendered inclusion of amphiphilic carrier redundant, which in turn implied easier scale-up under current good manufacturing practice (cGMP) for this technique. Another approach for making solid dispersions using SCF technology is by impregnation of polymer matrix with drug dissolved in SCF. Here, unlike the PGSS and GAS methods, solid solution or amorphous solid dispersions are obtained. The requirements for this process are that the solubility of high pressure CO_2 in polymer should be relatively high in order to swell the polymer, and the drug should be soluble in the supercritical CO_2 to make impregnation possible. SCF impregnation is based on the affinity of drug molecules to the polymer matrix and offers the distinct advantages of eliminating organic solvent and heat.[60] Amorphous drug polymer formulations were prepared free of drug crystallites successfully by impregnating ibuprofen into PVP. Dispersion of ibuprofen within the PVP matrix was possible via H-bonding of each drug molecule to the basic sites of the polymer.[61]

Another advantage of this method is that the amount of the impregnated drug can be controlled, and the process can be immediately stopped, by depressurizing the high-pressure cells once the desired level of impregnation is achieved. In addition, the process of impregnation that depends on the drug diffusion rate can be easily "tuned" by the pressure of the SCF solution, which influences the sorption and polymer swelling.[62]

SCF-based processes are widely used in the food industry and offer several advantages, both in general and compared with other methods of preparation of solid dispersions. The processing equipment can be totally enclosed, free of moving parts, and constructed from easily maintained high-grade stainless steel. Particle formation in a light-free, oxygen-free, and possibly moisture-free atmosphere minimizes their confounding effect during scale-up. Advances in understanding the mechanism of supercritical particle/coprecipitate formation and SCF mass transfer form the basis for efficient scale-up. Industrial units, such as Bradford Particle Design (Bradford, West Yorkshire, UK), have resources for the annual production of 1 ton of cGMP material. The cost of manufacturing in pilot scale with SCF technology is comparable with (or may be better than) conventional techniques such as single-stage spray drying, micronization, crystallization, and milling batch operations.[56] Given the advantages of SCF technology compared with other conventional methods, perhaps the only reason a product has yet to reach large-scale operations is manufacturers' unfamiliarity with the process.

CONCLUSION

The various technologies discussed have been successful in the laboratory as well as the scale-up. Some products have been marketed using technologies like the surface-active carriers. Hence these technologies are expected to form a basis for the commercialization of many poorly water-soluble and water-insoluble drugs in their solid-dispersion formulations in the near future.

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