Nanoparticle Engineering using Rapid Expansion of Supercritical Solutions

Shilpa S. Mahamulkar

Final Year B.Tech.
Pharmaceutical Sciences and Technology Department

Abstract

In the case of pharmaceutical substances the particle size is quite important since it can limit the bioavailability of poorly water soluble drugs. Nanoparticle formation has been proposed and utilized as a method to improve oral bioavailability of poorly soluble drugs. Since the mid-1980s, a new method of nanoparticle generation has appeared involving supercritical fluids. Carbon dioxide is the most widely used solvent and its innocuity and "green" characteristics make it the best candidate for the pharmaceutical industry. This article gives an overall view of the RESS (Rapid expansion of supercritical solutions) and its various modifications. It also provides the information and resources necessary for startup research involving particle formation using supercritical fluids. The various stages of particle formation by supercritical fluid processing can be broadly classified into delivery, reaction, pre-expansion, expansion and collection. The importance of each of these processes in tailoring the particle morphology is discussed here.

Keywords: nanoparticle, supercritical fluid.

1. Introduction

Technological advances in both biotechnology and molecular biology have yielded a surge in the number of new chemical entities that are produced to treat diseases or ailments. However, a growing portion of these chemical entities display poor aqueous solubility, leading to poor oral availability and an inability to form intravenous formulation [1]. Hence, the whole scenario still demands extensive research for developing innovative yet universal approach to tackle the problems associated with the delivery of hydrophobic drugs in order to improve their clinical efficacy and optimize their therapy[2]. A reduction in particle size generates a corresponding increase in surface area. A larger surface area creates a greater possibility for dissolution in a solvent, which can lead to significantly increased dissolution rates. Nanoparticle formation has been proposed and utilized as a method to improve oral bioavailability of poorly soluble drugs and as a method for delivery of particles via parenteral, pulmonary, and topical administration [1].

The nanosize of the nanoparticulate delivery systems allows crossing of biological barriers, ameliorates tissue tolerance and improves cellular uptake and transport, thus enabling efficient delivery of the therapeutic agents to the target sites like liver and brain [2].

Conventional processes for particle formation like milling, spray drying, precipitation from solution by the addition of an organic antisolvent suffer from limitations in producing a desirable end product. Thus, there is a need to identify alternative approaches to produce small particles for pharmaceutical use. Use of supercritical fluids (SCFs) has been an attractive alternative [4].

2. Supercritical Fluid (SCF) Technologies [5-8]

A fluid heated to above the critical temperature and compressed to above the critical pressure is known as a supercritical fluid. A supercritical fluid has densities similar to that of liquids, while the viscosities and diffusivities are closer to that of gases. Thus, a supercritical fluid can diffuse faster in a solid matrix than a liquid, yet possess a solvent strength to extract the solute from the solid matrix.

In contrast to the conventional particle formation methods, where a larger particle is originally formed and then comminuted to the desired size, SCF technology involves growing the particles in a controlled fashion to attain the desired morphology. Growing particles from a solution in a controlled fashion, on the other hand, means that the rigid solid particle, once formed, does not have to undergo the thermal and mechanical stresses. This feature makes supercritical fluid technology amenable to produce biomolecules and other sensitive compounds in their native pure state [9].

The following unique advantages offered by supercritical fluids acting as solvents or antisolvents allow a wide control of particle morphology[4]:

- Solvent properties that can be tuned by changing pressure and/or temperature,
- Reduced viscosities and increased mass transfer,
- Control of supersaturation via pressure, temperature,
- Low level of operating temperature (since in most cases carbon dioxide is the SF).

Supercritical technology produces high purity products with no

residual solvents; controls crystal polymorphism; makes possible processing of thermolabile molecules; is a single-step process; is an environmentally acceptable technology.

Carbon dioxide is regarded as a favorable processing medium and is the commonly used SCF for pharmaceutical applications. It is having a GRAS ('generally regarded as safe') status, is chemically inert, non-flammable, inexpensive, has a low critical temperature and pressure and exhibits solubilization effects that can be varied continuously by moderate changes in pressure and temperature [9]. It is the green solvent of 21st century.

Table 1: Critical Properties of Some Common Supercritical Solvents [10]

Solvent	T_c(K)	P_c(MPa)
Carbon dioxide	304.2	7.38
Trifluoromethane	299.0	4.80
Propane	369.8	4.24
Water	647.2	22.12

Until now, there are several methods for the formation of submicron particles. The RESS (rapid expansion of supercritical solutions) method of particle formation is discussed in this article.

3. Rapid Expansion of Supercritical Solutions (RESS)

The RESS process relies on the solvent properties of supercritical carbon dioxide. Because CO2 is a nonpolar molecule, this process will be mainly efficient and interesting for micronizing nonpolar molecules.

3.1. Basic Principles

The RESS-process consists mainly on two steps: the first one is the dissolution of the solute of interest in a suitable SCF. The second one is the sudden depressurization through a nozzle which produces small particles through precipitation with a narrow size distribution[3].

The gaseous solvent is cleaned in a column, condensed, sub-cooled and pressurized to the desired pressure with a diaphragm pump, and the mass flow rate is measured by a mass flow meter. When a co-solvent is used, it is pumped in the same way and introduced into the CO_2 flow. This flow is then heated to the desired temperature and allowed to enter a tank loaded with the active substance for extraction. In this part of the process, the solvent power is strong because of the high pressure and because of the possible presence of a co-solvent. This mixture is then depressurized in an expansion vessel by means of a capillary or a nozzle, with a typical inner diameter of 50 to 60μm. The expansion jet is sprayed always to ambient pressure and temperature. The particles are collected on a membrane filter and the gaseous solvent is vented. See figure 1.

3.2 Particle formation

In RESS, the material to be processed is dissolved at high pressure in a SCF (usually CO_2) and heated to the desired pre-expansion temperature (T_0). The unsaturated supercritical mixture is then

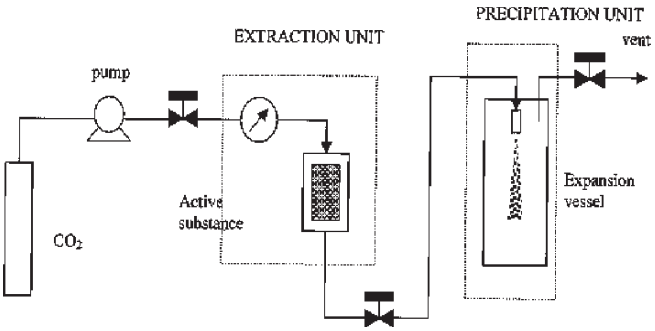

Fig.1. RESS Apparatus [11]

rapidly expanded through a nozzle to ambient conditions. The decrease in density brings appreciable supersaturation and produces fast nucleation. Prior to precipitation, the degree of supersaturation depends strongly on the solutes equilibrium mole fraction at the prevailing temperature and pressure during the expansion and hence on the phase behaviour of the respective binary mixture. When nucleation occurs, particles grow by coagulation, which is the growth by collision of particles, and by condensation, which is the deposition of molecules on the particles surface. Supersaturation influences nucleation and growth rates to different extents. The attained high supersaturation values (10^5 to 10^8) and hence high nucleation rates offer the potential to uniform crystal growth which enables the production of very fine ($< 1\mu$m) and solvent free particles with a narrow size distribution [3].

3.3 Experimental results

Experimental research on the RESS-process has been carried out for over 20 years and numerous publications have demonstrated that the RESS process enables the formation of drugs with particle diameters in the submicron range i.e. below 1ìm [3].

The experimental results published in literature can be summarized as follows [3]:

a) Influence of pre-expansion temperature (T_0): increasing T_0, at constant pressure, leads often to an increase in particle size.
b) Influence of pre-expansion pressure (p_0): increasing the pressure, at constant temperature, increases the CO_2 mass flow rate which decreases the residence time of the particles in the expansion chamber. This results in less time available for particle growth and therewith smaller particles.
c) Influence of nozzle diameter: increasing the nozzle diameter, at constant pre-expansion temperature and pressure, increases the CO_2 mass flow rate and leads therefore to smaller particles.
d) Solubility in SCF: a lower solubility results in smaller particles. The decrease of particle size with decreasing solubility is caused by the fact that particle collision rate is proportional to the square of particle concentration.

3.4. Limitations of the RESS process

The most obvious drawback of RESS is the fact that several families of molecules are not soluble in CO_2. One way to overcome this problem is to change the supercritical fluid. However, this is seldom possible since the few other candidate molecules (N_2O, light hydrocarbons) are much more hazardous and less environmental friendly than CO_2.

Another possibility is to use the RESS process with a co-solvent being previously dissolved in the CO_2. In this case, the advantage of not using any chemical solvent is lost, but this could be attenuated by using low-toxicity solvents like acetone or ethanol. The choice of the proper co-solvent is not trivial and the two-by-two affinity of supercritical fluid, co-solvent and solute are to be considered. A mixture of co-solvents may also be used [12].

Another problem is that the particles produced by RESS tend to agglomerate due to their adhesive nature. Hence, several modifications of the RESS process have been proposed to reduce the limitations leading to decreased particle size.

4. Modifications of the RESS process

4.1. RESS into aqueous solutions (RESAS) [14-16]

An interesting variation of the RESS process is the rapid expansion of a supercritical solution into aqueous solutions (RESAS). This technique has evolved in order to minimize the generation of micro particles observed due to increased coagulation rate in the free jet expansion of RESS. The process brings about expansion of supercritical solution through an orifice or tapered nozzle into aqueous solution containing a stabilizer in order to minimize the particle agglomeration. The stabilizers utilized in the process are mainly surfactants like polysorbate, poloxamers and lecithins which minimize the particle aggregation by rapidly reducing the surface of primary particle generated and by orienting itself to provide stearic stabilization. During the process, the supercritical solution containing drug is passed through a specially designed nozzle submerged 1 cm below the surface of aqueous surfactant solution. To avoid the generation of foam arising due to vigorous expansion of the CO_2 spray into the aqueous solution, N_2 is sprayed on the top [2]. (See figure 2.)

The effects of various parameters on the process are as follows [2, 14, 16]:

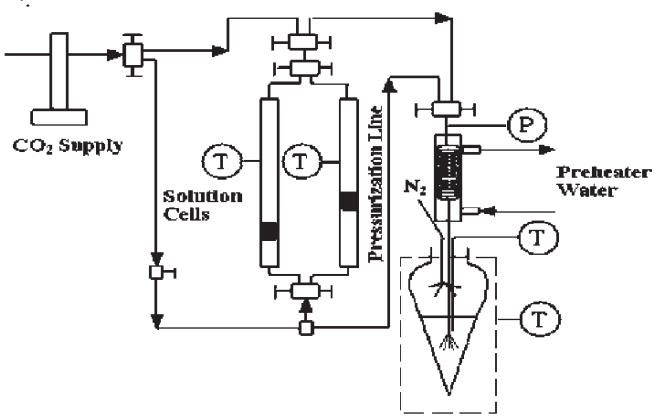

Fig.2 : RESAS Equipment [14]

4.1.1. Effect of Stabilizer

The type of surfactant employed in the process for stabilizing the nanoparticulate suspension has pronouncing effect on the particle size. The choice of stabilizer is specific to each drug candidate. In certain cases, even combination of stabilizers would be required in order to achieve optimum particles size and stability. The stabilizer should possess enough affinity for particle surface in order to give better stabilization [2]. See Table 2.

4.1.2. Effect of Drug-to-Surfactant Ratio

Table 2: Parameters of Ibuprofen Nanoparticles with Different Stabilizing Agents

Stabilization agent	Concentration (mg/ml)	Average size (nm)	Deviation (nm)
PVP (M_w~40000)	0.5	40	8.2
PVP (M_w~40000)	2	39	8.4
PEG (M_w~6000)	2	27.6	5.8
PEG (M_w~35000)	2	44	7.8
SDS	3.3	2.5	5

It is a factor that should be given due consideration as it will govern particle size as well as the stability of nanoparticulate suspension. An increase in the amount of surfactant aids stabilization of particle suspension. However, if concentration of surfactant becomes too large the formation of a large number of micelles could lead to substantial solubilisation of drug in cores of micelles [2].

4.1.3. Effect of Suspension Concentration

Suspension concentration has direct influence on the particle size. The particle size of final nanoparticulate suspension increases with the increase in suspension concentration [2].

4.1.4. Effect of Stabilizing Solution Temperature

Stabilizing solution temperature would also contribute to the drug loading and particle size mainly by influencing the phase transition temperature of the stabilizer [2].

4.1.5. Effect of Pre-heater Temperature

By varying the pre-heater temperature, the solubility and drug loading of the drug candidate can be modified. Due to the higher pre-heater temperature, during the depressurization in the nozzle, the solution will pass through the phase boundary more quickly than at lower pre-heater temperature, leading to higher levels of supersaturation. The greater supersaturation will, in turn, lead to higher rates of nucleation leading to formation of smaller particles[2].

4.1.6. Long Term Stability

The particles produced by RESS settle completely and cake at the bottom of the vial in which they are stored. These samples cannot be redispersed even by sonication. The samples produced by RESAS with stabilizer solution have good stability, with no settling observed for most of the suspensions without shaking. If some settling is present, the samples can be easily redispersed by gentle inversions[14].

4.2. RESS with a Solid co-Solvent (RESS-SC)

The often low solubility of pharmaceutical compounds (such as Griseofulvin) in sc-CO_2 results in a low processing rate. To overcome this drawback researchers have used various liquid co-solvents like acetone and ethanol to enhance the solubility. However, only small

amounts of liquid co-solvents are suitable for RESS due to the dissolution of particles in the expansion chamber.

Recently, a modification of the RESS process (RESS-SC) was proposed [18]. In the RESS-SC process, a solid co-solvent is used to enhance the drug solubility in CO_2 and avoiding surface-to-surface interaction to other drug particles and therewith hindering particle growth. Later, the solid co-solvent can be easily removed from the solute particles by sublimation [3].

In conventional RESS process, each particle is surrounded by same kind of particles (see Fig. 3a) in the expansion zone which results in larger particles due to coagulation. Rapid expansion of supercritical solution with solid co-solvent (RESS-SC), overcomes this particle growth in expansion zone resulting in smaller nanoparticles. In RESS-SC, drug particles are surrounded by a solid co-solvent as shown in fig. 3b, avoiding surface to surface interaction to other drug particles, hence hindering the particle growth. The co-solvent is simply removed by sublimation using a lyophilizer, which is carried out after the particle recovery from the expansion chamber [18]. Solid co-solvent should have sufficiently high vapor pressure for easy removal by sublimation; should be solid at nozzle exit conditions, should have appreciable solubility in sc CO_2; should be non-reactive with desired solute or sc CO_2, non-flammable, non-toxic, inexpensive[18].

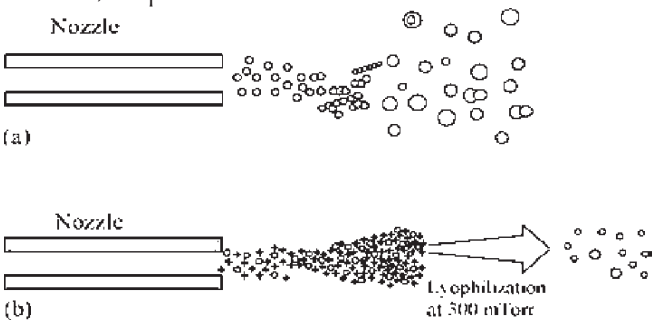

Fig. 3 : a) RESS Process b) RESS-SC [18]

In figure 4, Section I, P is a high pressure syringe pump for pressurizing CO_2 at desired pressure using CO_2 from cylinder A. Two vessels, M and S, are used as extraction column for solid co-solvent and drug, respectively, in Section II. Glass wool is used on both the ends of vessels M and S to avoid any undissolved material carry over with the CO_2 flow. Both vessels containing solute and co-solvent are kept in a water bath to keep constant extraction temperature (±0.1°C) by temperature controller. Section III is either an expansion chamber for RESS-SC experiment or a U-tube for solubility experiments and is kept at atmospheric pressure and ambient conditions. Valve V_1 connects Section I with Section 2 whereas valve V_3 connects Sections 2 and 3. Valves V_1 and V_2 are three-way valves for CO_2 bypass connection to vessel S to perform conventional RESS experiments for comparison. Glass wool is used at the end of the expansion chamber outlet or at the end of the second leg of the U-tube to entrap the particles. Temperature in the expansion chamber is recorded using a thermocouple [18].

4.3. RESS with a Biocompatible Polymer [19-21]

Among the large number of substances that have been processed with RESS, biocompatible and/or biodegradable polymers are of

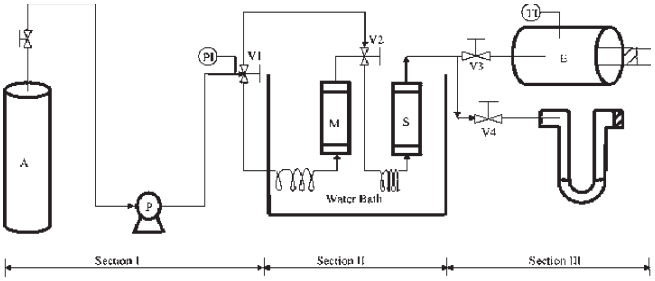

Fig.4. Schematic for RESS-SC Process [18]

pharmaceutical interest and significance since such submicron particles may be used as a carrier for drugs or proteins and for controlled release applications. Controlled release of parenteral doses can be achieved through the production of biodegradable nanoparticles that are used to encapsulate drug molecules, and these delivery systems can be delivered via intravenous, subcutaneous, or depot intramuscular injection [1]. The absorption of some poorly water-soluble drugs can be significantly improved by producing composite nanoparticles of the drug with water-soluble or certain biodegradable polymers or lipids. In the modification of the RESS process, both, the solute and the polymer are dissolved in sc-CO_2, followed by the rapid expansion of the ternary mixture. Thereby, the sudden depressurization leads to simultaneous co-precipitation of the solutes and formation of composite particles [3].

Besides the co-precipitation, drug-loaded polymer particles could also be generated by impregnating drug materials into polymer matrix. Composites of ibuprofen in the particles of α-lactose were produced by using RESS impregnation technique. The carbon dioxide solution containing dissolved ibuprofen was sprayed into a stirred vessel, at atmospheric pressure, where a known amount of the biopolymer particles was previously introduced. The precipitation of ibuprofen in the presence of polymer particles with the vigorous agitation allowed the impregnation of drug into the polymer. The dissolution rate of impregnated ibuprofen in the composite particles was found to be enhanced compared to plain drug particles [21]. See Table 3.

4.4. Drug/Carrier Inclusion Complexes

Table 3 : Formation of Polymer Particles that Incorporate Active Ingredients using Supercritical Fluids as Solvents (RESS) [21]

Polymer/Active ingredient	Solvent/Co-solvent
PCA, PLA/lysozyme, lipase	CO_2/ethanol
PLA, PEG, ethylcellulose/p-acetamidophenol, acetylsalicylic acid, flavone, 1,3-dimethylxanthine, 3-hydroxyflavone	CO_2/ethanol
Lipid/albumin	CO_2
Fluorinated polyacrylate/2,5-distyrylpyrazine	Chloroform/methanol
Lactose/ibuprofen	CO_2

Various techniques, such as kneading, grinding, co-precipitation, and freeze-drying, are used to incorporate poorly water-soluble substances into a fast dissolving hydrophilic carrier. However, most of these methods use organic solvents as media, which can be

found as residual in the product. Therefore, SCF-based preparation of inclusion complexes receives increased attention since such processes enable the preparation of solid complexes without organic solvents in a single processing step. The so-called CPD process (controlled particle deposition) is applied for the deposition of submicron particles in porous solid carriers. The key idea behind CPD is to dissolve the solute of interest in supercritical CO_2, followed by permeation of the supercritical solution into the pores of the (CO_2 insoluble) carrier (e.g. Cyclodextrin, CD) and precipitation of the drug inside the pores, caused by a sudden depressurization. CDs are widely used in drug formulation because they are able to form inclusion complexes with lipophilic drug molecules and improve aqueous solubility, dissolution rate, stability and increase the bioavailability of poorly water-soluble drugs [3]. See Table 4.

5. Design and Process Aspects of Laboratory Scale RESS

Table 4: Formation of Polymer Particles that Incorporate Active Ingredients using Supercritical Fluids as Solvents (RESS) [21]

Embedded material	Host structure
Piroxicam	α-CD
Miconazole, miconazole nitrate	α-CD, HPβCD, γ-CD
Ibuprofen	MβCD
Naproxen	α-CD
Itraconazole	α-CD

The various stages of supercritical particle formation can be broadly classified into supercritical fluid delivery, reaction, pre-expansion, expansion and collection and SCF recycling.

5.1. Supercritical Fluid Delivery

The most common and economic route of reaching the supercritical region is from a gas through the liquid state into the SCF phase. Compressed CO_2 is readily available in large quantities with a high level of purity and is reasonably priced. This is liquefied by passing through cooling lines prior to charging the pump. Delivering the fluid to the pump in a liquid state ensures effective pressurization without any cavitation problems. Frictional forces from the pump and the heat of compression can raise the temperature of the fluid, thereby inducing phase change and needs to be compensated using a heat exchanger. Pressurized liquid from the pump is then brought to the supercritical state by passing through a heat exchanger (pre-heater). Owing to the high thermal conductivities of these fluids, supercritical temperatures are easily reached although the residence time of fluids in the pre-heater is not long. A lengthy piece of coiled tubing up to 5m in length is typically used as a heat exchanger to raise the temperature of compressed CO_2 (1–5°C) to supercritical state (>31°C). The temperature of the coil is controlled using either a temperature bath/oven or a heating tape and is chosen such that equilibrium supercritical temperatures are attained by the time the fluids exit the coil.

Steady flow rates of SCFs assist in creating uniform conditions for nucleation and are therefore of interest in the context of particle formation. Wherever uniformity in flow rates is considered important, pulse dampeners can be used to buffer these pulsations. The fluid mixture can then be delivered to the pre-heater that raises the temperature of the resulting mixture to the supercritical state [9].

5.2. Processing

The processing vessel (also called as pressure vessel or a reaction vessel) is where the supercritical fluid is brought in contact with the material(s) to be processed. Essential requirements for a processing vessel are chemical inertness, ability to withstand the operating temperature and pressure conditions. Pressure vessels made for pharmaceutical applications are typically made of stainless steel (316 SS) due to the sturdiness and chemical inertness of the material.

The temperature of the vessel can be regulated either by using a heating mantle or a temperature-controlled bath/oven. Loss of pressure upstream of the point where the supercritical fluids are depressurized is compensated by using a backpressure regulator (BPR). A common problem seen with the use of backpressure regulators in SCF particle formation processes is the precipitation of solutes and/or dry ice (in $scCO_2$ applications) in the BPR. Joule–Thompson cooling as a result of the large volumetric expansion across the BPR leads to drop in temperature of the supercritical solutions and is the cause for such precipitations. This leads to inconsistent flow rates on one end and plugging of the lines in severe conditions. Independent temperature control of the BPR is therefore essential to prevent such problems.

Mixing the material with glass beads (e.g. 10/90% by weight of material/glass beads) and glass wool prior to loading it to the processing vessel is used to improve the degree of interaction between the supercritical fluid ant the material to be processed [9].

5.3. Pre-expansion

The composition and phase of the supercritical solution from which the particles precipitate are found to have a major effect on the particle morphology in RESS. Independent control of the temperature and pressure during the pre-expansion stage is therefore critical in these processes. Additionally, the phase changes in the supercritical solutions, which often lead to plugging of the lines, can be eliminated through the use of a controlled pre-expansion line. The composition of the solution in this line may not only be controlled by changes in temperature, but also by adding fresh SCF solvent to the line. It is usually maintained at approximately 50°C higher than the temperature of the reaction vessel using a heating tape or a temperature oven [9].

5.4. Spray Configuration

A restriction device is designed to support the large pressure drop that occurs across it, while maintaining suitable conditions for precipitation. In RESS processes, the device controls the growth of particle after the nucleation process by affecting the dynamics of jet expansion. Joule–Thompson cooling, resulting from the large volumetric expansion across the restriction device causes a drop in temperature, thereby affecting a phase change and subsequently leads to plugging of the device. The restriction devices are therefore heated to compensate for such effects. While stainless steel nozzles are most frequently used owing to their strength to withstand the large pressure differential, they are limited by their poor thermal

conductivities. Wherever necessary, they can be replaced with sapphire nozzles that provide better heat transfer to the fluid while also maintaining the material strength [9].

5.5. Particle Collection

Retaining the original characteristics of the particles produced by supercritical fluid process is as critical as forming the particles and constitutes the particle collection step. This step is critical in that the distinct characteristics of the particles can be completely lost owing to a poor collection technique. In rapid expansion of supercritical solutions, the rapidly expanding supercritical fluids impart high kinetic energies to the particles produced. Insufficient path for expansion can therefore result in the agglomeration of particles. The agglomeration is even worse in the presence of residual amounts of co-solvent in RESS process. Design of particle collection vessel in these processes should be such that agglomeration is kept to a minimum by providing a sufficient path for expansion of the supercritical fluids. The potential designs of particle collection involve the use of high-efficiency filters, cyclone separators and electrostatic precipitators [9].

Particles suspended in a liquid medium can be recovered using filtration, assuming that the filter pore size is smaller than the particles[9].

Liquid scrubbing is also known as one of the most efficient methods for very fine-particle collection, but they are gathered in the form of a suspension that can be rather used for nasal, pulmonary, or parenteral delivery [4].

5.6. Recycling

In all large-scale plants, the fluid is recycled for obvious economical and ecological reasons. This means that the separation of solute(s) from the fluid prior to its recycling must be as perfect as possible to avoid deposition throughout the recycle loop that may lead to plugging and stopping the unit for a long time. The commercial viability of a technology depends not only on its scientific virtues but also on the cost of instrumentation and operation. The rapid change in the solvent strength of SCFs with moderate adjustments in pressure and temperature, in theory, can be utilized to recover the supercritical fluid [9].

5.7. Fluid Disposal

When active substances are processed, no direct fluid disposal is acceptable and the depressurized gas can be vented to the atmosphere only after treatment. In most cases, the active substance that may be carried out by the gaseous effluent is solid and filtering is efficient. In rare cases, when the active substance is present in the form of an aerosol, water scrubbing is required [4].

5.8. Safety

Carbon dioxide is considered a GRAS (generally regarded as safe) solvent with a TLV-TWA value of 5000 ppm. (TLV-TWA is the threshold limit value time weighted average concentration for a normal 8h workday or 40 h workweek, to which all healthy workers may be repeatedly exposed, day after day, without adverse effect). While this is otherwise not an issue, combinations of CO_2 along with other solvents may pose a risk and can be addressed through the use of proper hardware combined with adequate shielding. The operational temperatures in SCF particle formation are lower compared to several other pharmaceutical operations. Burn-related hazards are therefore infrequent while dealing with SCF particle formation. SCF particle formation operations not only require the use of hardware rated for high pressures, but also the employment of multiple pressure-relief mechanisms and safety practices [9].

6. Future perspectives

In future, various techniques can be used for enhancing the atomization. Some of them have been listed below.

- Atomization using ultrasonic processor
- Atomization using centrifugal disks
- Atomization using electro-spraying

7. Conclusion

RESS is a very attractive and simple process for the production of submicron and uniform particles with improved dissolution behaviour. The advantages of SCFs, such as the solvent-free product, low temperature, small particle size, uniform size distribution, and less processing steps, have promoted the particle and product design by RESS. However limitations of RESS are as follows:
(a) the low solubility of polar drugs in sc-CO_2 and
(b) the small particles which tend to agglomerate due to their adhesive nature.

In order to overcome these drawbacks various researchers developed different modifications of the RESS process. These modifications include the use of surfactants and water-soluble polymers as stabilization agent for the produced nanoparticles, the use of a solid co-solvent, the formation of drug/polymer composite particles, and the preparation of inclusion complexes.

Particle formation using SCFs as a continuous unit operation is conducted in an enclosed system. A majority of the off-the-shelf SCF instrumentation is designed for extraction purposes. Only a selective few vendors appear to be in the early stages of manufacturing equipment designed for particle formation. The scarcity of information on the design and process engineering of laboratory scale equipment is recognized as a significant shortcoming to the technological progress. This article therefore provides the information and resources necessary for startup research involving particle formation using supercritical fluids.

I have given a seminar on this topic under the guidance of Dr. (Mrs.) Vandana Patravale, faculty of Pharmaceutical Sciences and Technology, ICT.

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