Particle formation by rapid expansion from solution using near-critical dimethyl-ether

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Abstract

The present experimental work examines the use of dimethyl-ether (DME) in a process for formation of particulate materials. DME is used in the sub-critical liquid state as a solvent which partially vaporizes as it is sprayed through a nozzle and then evaporates to leave a fine, dry, solvent free powder. DME is an effective solvent for a range of polar compounds, including many pharmaceutical compounds, and good product throughput rates can be achieved. The spray characteristics are investigated here in terms the hydrodynamics and thermodynamics of the depressurization step, and using a visual analysis of the profile of the spray. The process is demonstrated using acetaminophen as a model solute, and the resulting particles are characterized by SEM analysis and measurement of their dissolution rate in water. Measurements of the solubility of acetaminophen in DME are also reported.
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1. Introduction

A large number (41%) of potentially effective active compounds are abandoned before being launched on the market due to poor biopharmaceutical properties, and in particular poor water solubility [1]. Thus, pharmaceutical industries currently face the challenge to design new bio-available systems. Since new functions arise from reducing the particle size of particulate materials, such as improved solubility and targetability or adhesion to tissues, micronization of pharmaceuticals compounds is a promising route to improving their commercial viability [2,3].

Supercritical fluids, and in particular supercritical carbon dioxide, offer a number of potential processes for generation of particles for the pharmaceutical industry [4]. Among the supercritical processes, the rapid expansion of supercritical solution process (RESS) is attractive; it is a simple process that enables generation of solvent free micro- or nanoparticles [5], without the need for aggressive solvents or drying processes.

Briefly, the RESS process consists of solubilising the solute to be micronized in a supercritical fluid under pressure. The saturated supercritical fluid is then rapidly expanded through a spraying device into an atomization chamber. The depressurization step causes super saturation and nucleation of the solute. The solvent evaporates and dry solvent free particles are collected. Because the depressurization step is a fast one, the growth of crystals can be limited and small nano or micro sized particles can be obtained [6].

Carbon dioxide is the most widely used supercritical fluid for pharmaceutical applications, in particular because of its low critical temperature and environmental friendly properties, and so far more than 98% of applications have been developed with this gas [7]. A range of active compounds have been processed using a CO_2 RESS process, such as antibiotics, statins, and sterols [8,9] but Perrut and Clavier [10] suggest that the RESS process is only likely to be commercially viable if the solubility of the active compound is higher than 10^{-3} kg/kg supercritical fluid. Many compounds have a lower solubility than this in CO_2, and this is likely to be a limiting factor in the extensive development of the RESS process; to date there are only a limited number of industrial applications using CO_2. Other super- or near-critical fluids, such as for example light hydrocarbons, hydrofluorocarbons, or dimethyl-ether, offer different solvent properties and may be effective alternatives to the use of CO_2.

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1.1. Properties of dimethyl-ether

Dimethyl-ether (DME) is largely used in the chemical industry as an assistant solvent, as a propellant gas in aerosol products, and as a refrigerant. It is also a potential alternative fuel for use in cleaner burning diesel engines. DME is gaseous under atmospheric conditions, with a boiling temperature of 248 K, and a vapour pressure at 293 K of 5.0 bar. Its critical temperature is 400 K and its critical pressure is 53.6 bar [11]. DME has a high polarity, and by controlling both pressure and temperature is has been shown that the solvent power of DME can be shifted over a range of 10 units on the Middletown solvent polarity scale [12]. This corresponds to a variation from a low polarity solvent to a polar one comparable to dimethylsulfoxide. A limited amount of data has been published on the solubility of compounds in liquid DME. Bausch et al. [13] report the solubility of several pharmaceuticals in DME and in CO_2. The units are given as "% g/V" and not clearly defined but comparisons at similar conditions give the solubility of Orlistat as 0.6% g/V in CO_2 (303 K, 100 bar, density $\sim$800 kg/m^3) and 17.8% g/V in DME (293 K, 4.5 bar, density $\sim$650 kg/m^3). The solubility of Saquinavir was less than 0.1% g/V in CO_2 (318 K, 200 bar, density $\sim$800 kg/m^3) but was measured above 10% g/V in DME (298 K, 100 bar, density $\sim$650 kg/m^3). Bosentan was soluble at less than 0.1% g/V in CO_2 (318 K, 200 bar, density $\sim$800 kg/m^3), whereas its solubility was 9% g/V in DME (318 K, 200 bar, density $\sim$650 kg/m^3). Wenclawiak et al. [14] measured the solubility of some polycyclic aromatic hydrocarbons in DME. The solubility of 1-methylnaphtalene was 0.32×10^{-6} g/g in a mixture of CO_2 and 10% by volume toluene, whereas this solubility reaches 1.11×10^{-6} g/g in DME.

1.2. Particle formation using DME

A significant factor influencing the morphology of the particles resulting from a RESS process is the characteristic of the spray. This determines the rate of supersaturation and the degree of dispersion of the resulting product, and depends on the shape of the nozzle, processing temperatures and pressures, and the thermodynamics of the solvent system. In this current work DME is used slightly below its critical temperature to ensure that the temperatures used do not exceed the thermal stability limits of the bioactive compounds being processed. As such, the solution passes through a liquid to vapor phase transition as it depressurizes through the spray nozzle. The spray emerges at a pressure below its vapor pressure and rapid partial vaporization (flash atomization) of the fluid stream occurs, followed by evaporation of the residual droplets. The process is distinct from the RESS process in this regard and is referred to here as the expansion of a flash boiling solution process (EFBS). The process offers many of the potential advantages of a RESS process, including rapid atomization and use of a solvent that is gaseous and easy to remove under benign atmospheric conditions. By operating close to the critical temperature the density and enthalpy differences between the liquid and gas states are small and similarities in behaviour to a RESS process can be obtained.

The characteristics of a DME spray from a nozzle are well reported in the automotive industry literature, because of the potential use of DME, and other oxygenated low molecular weight fuels, as a much cleaner fuel for combustion engines. The shape of the spray and the size of the droplets formed are important to good combustion. DME nozzle sprays are characterized qualitatively, for example, by Hwang et al. [15] and Suh et al. [16]. Wu et al. [17] also describe the spray patterns of dimethoxymethane and dimethylcarbonate, which have similar physical properties to DME. Compared to diesel the fuels have a viscosity that is a factor of 20 lower, and the sprays generally have a wider spray angle and smaller surface mean droplet size. Sauter mean droplet sizes of around 20–30 μm are observed, which increases with increasing nozzle diameter and ambient (downstream of nozzle) pressure. A summary of correlations to predict the penetration length of the spray is given by Kim et al. [18]. The nozzle sprays described in these papers are in the partial flashing, or flash boiling, region that is of interest to the current investigation when the temperature in the expansion chamber is sufficiently high and/or the downstream pressure sufficiently low to be above the vapour pressure of the fuel. The sprays of interest to the automotive industry are however of very short duration and are not directly comparable to the steady state spray profiles of interest in this work.

A model for the flash boiling spray process is described by Senda et al. [19]. The model incorporates modeling of the nucleation of bubbles of the gas phase as the flow approaches the spray nozzle, expansion of these bubbles in the liquid phase as the free jet expands and the liquid phase cools down, and breakup of the liquid stream into evaporating droplets. The key prediction of initial bubble nucleation rates is however fitted to experimental measurements for their system, and the jet breakup is applied to a hollow cone spray nozzle geometry.

In this current work, the spray of a DME liquid stream is investigated under conditions where the downstream pressure is below the vapor pressure of the DME and flash boiling of the spray occurs. The extent of the spray before complete evaporation occurs is observed, as this is an important factor in determining the size of the expansion vessel required to prevent wetting of the walls of the vessel and enable precipitation of a dry powder. The breakup of the spray and size of the droplets formed is also important for predicting the size and morphology of the particles produced. To demonstrate the application of this process to particle formation, results for precipitation of acetaminophen from a DME flash boiling spray are presented. A recent study has shown that the dissolution rate of acetaminophen could be enhanced by supercritical anti solvent crystallization [20]. The solubility of acetaminophen in DME is also reported.

2. Investigation of DME spray through a nozzle

Conventional theory for the breakup of a liquid jet passing through a nozzle [21] describes the breakup due to hydrodynamic forces on the surface of the liquid jet, and classifies it into regimes based on the Reynolds number, and the ratio of the viscous to hydrodynamic forces represented by the Ohnesorge