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Selection of Solvent in Supercritical Antisolvent Process

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Abstract

Supercritical antisolvent process (SAS) is widely being used to micronize the pharmaceutical compounds. The advantage of SAS process is that thermal degradation does not occur in the pharmaceutical compounds as the operating temperature is near to room temperature. This process starts with the atomization of a solution, a mixture of pharmaceutical compound and solvent, in the supercritical carbon dioxide environment. The transfer of carbon dioxide (antisolvent) to the droplet decreases the solubility of solute in the solution causing precipitation of solute in micro to nano-particle size range. In this work, four solvents: dimethyl sulfoxide, ethanol, acetone and dichloromethane have been considered to study the effect of solvent on droplet diameter, solvent mass transfer rate into supercritical carbon dioxide environment and velocity profile. The atomized droplet moves downward and mass transfer takes place. Two film theory of mass transfer has been used to calculate the molar flow rate of solvent into supercritical environment and carbon dioxide into droplet. Due to this two way mass transfer, composition of the droplet and thus size is changing continuously. The size of the droplet is calculated assuming that the droplet remains spherical during its downward movement. The size depends on the total number of moles in the droplet and molar density. Peng-Robinson equation of state has been used to calculate the molar density. The velocity profile of droplet is calculated using force balance equation on a moving body in a medium. Result shows that dichloromethane is the best solvent as it has small initial droplet diameter and less residence time compare to other solvents.

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1. Introduction

There has been a lot of interest in scientific community to reduce the particle size of pharmaceutical compounds to increase their bioavailability. Traditionally this size reduction is being done by milling, grinding, and spray drying and liquid antisolvent process. But these traditional processes have some disadvantages such as broad particle size distribution, degradation of product by mechanical or thermal stress or contamination due to the residual solvent. Therefore new techniques are being explored to overcome these disadvantages. One of the new methods explored is the use of supercritical fluid in micronization process. Supercritical fluids have unique properties such as gas like diffusivity and liquid like density and these properties have been exploited to overcome these disadvantages [1].

Supercritical fluid (SCF) micronization processes are classified according to the role of supercritical fluid in the process. SCF may act as a solvent or antisolvent depending upon the solubility of pharmaceutical compound in supercritical fluid. When SCF acts as a solvent then the process is called Rapid Expansion of Supercritical Solution (RESS). This method is used when solute is soluble in the supercritical fluid. In this method, the solute is solubilized in the supercritical fluid and then it is expanded. As the supercritical fluid expands, it comes to gaseous state and solute is not soluble in the gaseous state thus leading to precipitation.

The pharmaceutical compounds which are not soluble in supercritical fluid are micronized by supercritical antisolvent process. In SAS process, solute is first dissolved into an organic solvent and then this solution is sprayed into the supercritical fluid environment. At supercritical conditions, the organic solvent and SC fluid are highly miscible. Thus, the SCF mixes with the organic solvent and thus solvent power decreases rapidly. This leads to precipitation of the solute.

Carbon dioxide is widely used as the supercritical fluid in supercritical fluid based micronization process. From Table 1 [2] it is clear that using supercritical (SC) CO_2 as an antisolvent allows pure product to be generated at mild operating conditions because the critical temperature and pressure of carbon dioxide are $31.1^{\circ}C$ and 7.38 MPa, respectively. Further carbon dioxide is least expensive, nontoxic and nonflammable.

Table 1. Critical properties of some compounds

Compound	T_c (K)	P_c (MPa)
Ammonia	405.7	11.3
Benzene	562.2	4.9
Carbon dioxide	304.3	7.4
Ethane	305.6	4.9
Ethylene	282.5	5.1
Methanol	513.7	7.9
n-Propane	367.0	4.3
Water	647.6	22.1
Xenon	289.7	5.84

2. Mathematical Model Formulation

In supercritical antisolvent process, the solute is first dissolved in a solvent and then this solution is sprayed into a precipitator in which carbon dioxide is at supercritical condition. This spray leads the droplets formation in the precipitator where mass transfer between the droplet and carbon dioxide take place. The simultaneous diffusion of CO_2 into the droplet and the evaporation of solvent from the droplet cause swelling of the droplet which may be followed by shrinking [3]. Moles of carbon dioxide diffusing into the droplet and moles of solvent coming out of the droplet is calculated using two film theory of mass transfer.

2.1. Droplet diameter

The initial droplet size in this work is calculated by the equation of Mugele cited by Mukhopadhyay [3] and given below.

$$d_0 = 5d_n \left(\frac{d_n \rho_L v_i}{\mu_L} \right)^{-0.35} \left(\frac{\mu_G v_i}{\sigma_L} \right)^{-0.2} \tag{1}$$

where d_n is the diameter of the nozzle, ρ_L is the density of the liquid in kg/m^3, v_i is the initial velocity of the droplet, σ_L is the surface tension of solvent and μ_L & μ_G are the viscosities of liquid & vapor phases respectively.

The density of the liquid is calculated using Peng-Robinson equation. The viscosity of liquid is calculated by Lucas method [4] and the viscosity of gas, which is supercritical carbon dioxide, is calculated using the correlation developed by Altunin and Sakhabetdinov [5]. The surface tension of the liquid is calculated is using Bock and Bird correlation [4]. The calculated values of viscosity, surface tension and initial droplet diameter for dimethyl sulfoxide, acetone, ethanol and dichloromethane are reported in Table 1.

As the droplet moves, its diameter changes due to mass transfer. At any time, the droplet diameter can be calculated by the following expression considering that droplet is spherical in shape.

$$d = \left(\frac{6N_{tot}}{\pi \rho_M} \right)^{1/3} \tag{2}$$

Where N_{tot} is the total number of moles in the droplet at any time t and ρ_M is the molar density in kmol/m^3. The total number of moles is calculated by the following expression

$$N_{tot} = N_0 + \pi d^2 (N_1 - N_2)\Delta t \tag{3}$$

where N_0 is the initial number of moles in the droplet and d is the diameter of droplet, N_1 is the moles of carbon dioxide diffused into droplet and N_2 is the moles of solvent coming out of the droplet in a time interval Δt.

2.2. Mass Flux of SC CO$_2$ and Solvent

The mass transfer between supercritical carbon dioxide and solvent is calculated using two film theory. According to two film theory, the expression of mass transfer can be written as follows:

$$N_1 = k_L (C_{L,1}^i - C_{L,1}) = k_L (\rho_L x_1^i - \rho_L x_1) \tag{4}$$

Where $C_{L,1}^i$ and x_1^i are the interfacial concentration and mole fraction of the CO$_2$ and N_1, the molar flux of CO$_2$ in kmol/(m^2.s). The liquid film mass transfer coefficient at supercritical conditions is estimated by the following correlation [6]

$$k_L = \left(\left(1.13 \sqrt{\frac{D_L}{t}} \right)^2 + \left(6.58 \frac{D_L}{d} \right)^2 \right)^{0.5} \tag{5}$$

where, D_L is the diffusivity of gas in liquid phase and d is the diameter of the droplet.

The rate of transfer of solvent vapor is estimated from the fluid phase concentrations at the interface and in

the CO_2 continuum (pure SC CO_2) by using the following equation:

$$N_2 = k_G(C_{G,2}^i - C_{G,2}) = k_G(\rho_G^i y_2^i - \rho_G y_2) \qquad (6)$$

where $C_{G,2}^i$ and y_2^i are the interfacial concentration and mole fraction of the solvent and N_2 the flux of solvent vapor in kmol/(m^2.s). The mass transfer coefficient in the continuous phase surrounding was estimated using correlation proposed by Hughmark [6] for rigid spheres in a flowing liquid or gas.

$$k_G = \left(2 + 0.463\left(\frac{\rho_L v d}{\mu_L}\right)^{0.484}\left(\frac{\mu_v}{\rho_L D_G}\right)^{0.339}(d\,g^{0.333}D_G^{-0.667})^{0.072}\right)\frac{D_G}{d} \qquad (7)$$

2.3. Velocity of the Droplet

Three forces act upon the moving droplet: its weight, the buoyancy, and the viscous friction. The following relation is obtained from the momentum equation written for a single droplet [7].

$$\frac{dv}{dt} = \left(\frac{\rho_L - \rho_G}{\rho_L}\right)g - \frac{18\mu_v v}{\rho_L d^2} \qquad (8)$$

where ρ_L and ρ_G are the densities of the liquid and gas phases, d is the drop diameter, v is the drop velocity and μ_G is the viscosity of the gas.

3. Results and Discussion

MATLAB has been used to solve the model equations listed above. The droplet journey has been discretized in small time intervals. In each time interval, the moles of carbon dioxide flowing into the droplet and moles of solvent coming out of the droplet is calculated. Thus, the total number of moles is calculated in the droplet. Once the moles are known, then mole fraction of carbon dioxide and solvent is calculated which then is used in Peng-Robinson equation to calculate the molar density of the droplet. Using molar density and total number of moles, the diameter of the droplet is calculated in its journey from the top to bottom of the chamber.

Table 2. Transport Properties and Initial droplet diameter for various solvents

Solvent	Viscosity (Pa-s)	Surface Tension (N/m)	Diffusivity (m^2/s)	Initial droplet diameter (μm)
Dimethyl Sulfoxide	1.6×10^{-3}	0.0466	2.9831×10^{-8}	259
Acetone	2.9183×10^{-4}	0.0221	3.4594×10^{-8}	133
Dichloromethane	3.905×10^{-4}	0.0238	2.8587×10^{-8}	121
Ethanol	8.5266×10^{-4}	0.0357	3.884×10^{-8}	209

3.1. Effect of Solvent on droplet diameter

Droplet diameter in supercritical antisolvent process changes due to mass transfer between carbon dioxide and solvent. The change in droplet diameter is different for different solvent due to different mass transfer rate

and transport properties. Fig. 1 shows the droplet dynamics for dimethyl sulfoxide (DMSO), acetone, ethanol and dichloromethane (DCM). It is clear from Fig. 1 that during the droplet downward movement, its diameter first increases and then decreases. The increase in the diameter is due to the high dissolution rate of carbon dioxide into droplet. After reaching the maximum diameter, the droplet starts shrinking due to back diffusion of carbon dioxide. This back diffusion of carbon dioxide from droplet to supercritical environment is caused by concentration difference of carbon dioxide.

3.2. Effect of solvent on residence time of droplet

Solvent is continuously evaporating from the moving droplet. When the solvent is evaporated completely from the droplet, no crystallization takes place in the droplet as there is no solvent. This time is called resident time in this work. Fig. 2 shows the evaporation profile of different solvents with respect to time. It is clear that the lowest residence time occurs in the case of dichloromethane followed by acetone, ethanol and dimethyl sulfoxide.

3.3. Effect of solvent on velocity of droplet

There is a change in the velocity of droplet as it moves down in the precipitator. Fig. 3 shows the velocity profile of droplet for different solvents in the precipitator. It is clear from the figure that high initial droplet diameter plays a key role in determining the droplet dynamics. The fall in velocity of high droplet diameter is less rapid as comparison to the smaller diameter. The droplet dynamics of acetone and dichloromethane are almost same because their initial droplet diameter does not differ much. But in the case of ethanol and dimethyl sulfoxide, dynamics changes largely due to the difference in the initial droplet diameter for these solvents.
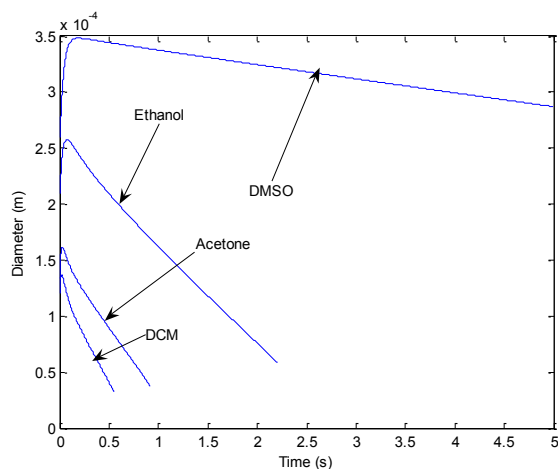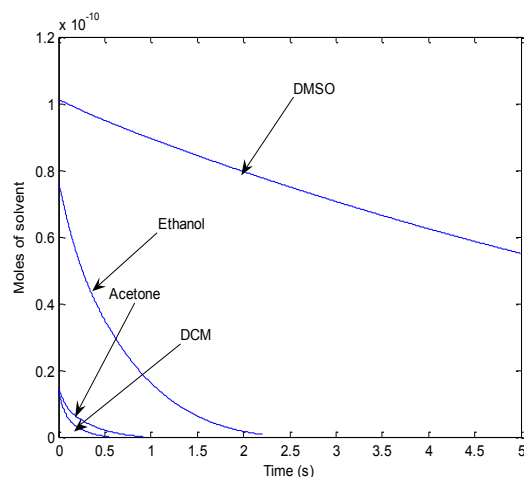
Fig. 1. "Droplet Diameter v/s time"
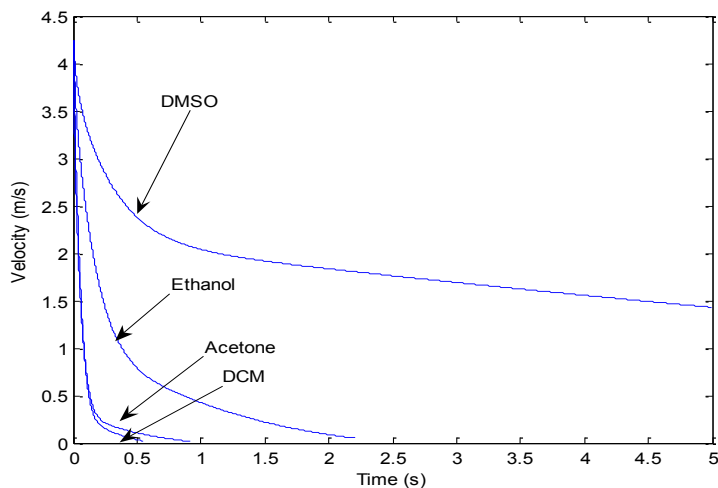
Fig. 2. "Moles of solvent v/s time"

Fig. 3. "Velocity v/s time"

4. Conclusions

The effect of solvent viz dimethyl sulfoxide, ethanol, acetone and dichloromethane has been studied on the diameter, residence time and velocity of the droplet. Initial droplet diameter is calculated for each solvent and it has been found that dimethyl sulfoxide has the largest initial diameter which is due to its high viscosity. The droplet diameter is found to change from top to bottom and attains a maximum at some intermediate distance. The residence time is different for different solvents. Dimethyl sulfoxide has the highest residence time because its initial droplet diameter is largest and hence it has more solvent to evaporate. The velocity profiles of different solvents show that there is a sudden fall in the velocity of dichloromethane and acetone compared that for to ethanol and dimethyl sulfoxide. Thus, it can be concluded that dichloromethane is the best solvent among all the solvents studied because it has smaller initial diameter and least residence time.

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