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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.

Keywords: Supercritical carbon dioxide, Dimethyl Sulfoxide, Ethanol, Acetone, Dichloromethane

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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°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.