SCF Application #526

The Micronization of Drug Particles by the Rapid Expansion of a Supercritical Solution

Introduction

A common problem in the pharmaceutical industry is that many drugs demonstrate poor solubility in water. Drugs that exhibit slow dissolution rates are less effective because they cannot quickly absorb into the gastrointestinal tract.

Typically, the pharmaceutical industry uses micronization techniques to increase the dissolution rates of drugs into biological fluids. Particle size reduction methods include recrystallization of the solute particles from solutions using liquid antisolvents, along with labor intensive techniques like crushing, milling, grinding, freeze drying, and spray-drying. Problems with traditional methods include the use of large amounts of solvent, solvent residues, broad particle size distributions, as well as thermal and chemical degradation of products.

The rapid expansion of supercritical solutions (RESS) is an alternative technique for the micronization of particles using supercritical CO_2 to quickly and naturally reduce the particle sizes of various drugs. Micronization by RESS involves dissolving a drug compound in a supercritical fluid, and then reducing the pressure across an expansion devise. The rapid depressurization of the supercritical phase causes decreased solubility of the solute, and precipitation of the solute as a powder in a gas phase. The result of the process is the formation of fine particles with a narrow size distribution without the use of solvents or surfactants.

Equipment

- ✓ Applied Separations' Helix Supercritical System

Method

Pack the dissolving vessel with the drug compound and install vessel on the Helix. Dissolve the drug in supercritical CO_2. Open outlet of dissolving vessel to discharge the supercritical solution through a nozzle into the crystallizer vessel.

Helix Conditions

The following RESS conditions were used in the micronization of ibuprofen.

Dissolving Vessel

Vessel:	100 mLs
Sample:	5 g
Pressure:	200 BAR
Temperature:	35°C
CO_2 Flow Rate:	0.6 L/h
Dynamic Time:	60 minutes

Crystallizer Vessel

Pressure:	Atmospheric
Temperature:	20°C
Nozzle:	50 micron x 1cm
Nozzle temperature:	100°C
Collection Technique:	Glass slide and 2 micron filter

Analysis

Scanning electron microscopy

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Results

Pharmaceutical Examples using RESS/CO_2

Compound	Particle Size (microns)
Aspirin	2 – 5
Caffeine	3 – 5
Cholesterol	2.3
B-Estradiol	<1
Ibuprofen	<2
Lidocaine	0.1
Nifedipin	1 - 3
Theophyllin	4 – 12

Conclusion

RESS produced ibuprofen particles with a median size of 2.5 micron and a narrow particle distribution. Micronization of drug compounds by RESS using CO_2 as a supercritical solvent can significantly increase the rate of dissolution of drug particles. RESS is a viable alternative to conventional methods of micronization, providing comparable results in the reduction of particle size and degree of crystallinity without the problems associated with mechanical grinding and solvent-based procedures.

References

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