# SUPERCRITICAL FLUIDS IN THE PHARMACEUTICAL INDUSTRY

SUPERKRITIČNI FLUIDI U FARMACEUTSKOJ INDUSTRIJI

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# Introduction

- Supercritical fluids technologies in chemical processes have attracted much attention in recent years finding wide application also in pharmaceutical field.
- Amongst supercritical fluids (SCF-s), scCO2 (Tc = 304.15 K and Pc = 7.38 MPa), and mixtures containing high amounts of scCO2, are undoubtedly the most used SCF-s.

- Other SCF-s of interest that have been tested in different applications are ammonia, hydrocarbons (such as ethane, propane, isobutane, ethylene, propylene, pentane, hexane, cyclohexane), fluorinated hydrocarbons (such as dichloromethane, difluoromethane,trifluoromethane, chlorodifluoromethane, pentafluoroethane, 1,1,1,2-tetrafluoroethane and 1,1,1,3,3,3-hexafluoropropane), ethanol, methanol, isopropanol, acetone, dimethyl ether, diethyl ether, nitrous oxide, sulfur hexafluoride and water.

- Supercritical $CO_2$ extractions have been widely used to separate and fractionate the valuable compounds in pharmaceutical processes [5, 10].
- SCF technology has been applied to drug formulation for the past 30 years and is now acknowledged as being a real alternative to conventional techniques using liquid organic solvents.
- Supercritical fluids have been applied to micronization pharmaceutical.

- The micronization by SCFs process has developed to rapid expansion of supercritical solution (RESS), gas antisolvent process (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical process (SEDS), aerosol solvent extraction system (ASES), supercritical fluid extraction of emulsions (SFEE), and particle from gas saturated solution process (PGSS).
- In RESS process, the supercritical fluid is solvent.
- When the GAS, SAS, SEDS, ASES, and SFEE process are used, the supercritical fluid is

# Methods for micronization by supercritical fluids

- ***Rapid expansion of supercritical solutions (RESS) process***

The principle of the RESS process is that the substance which has to be powdered is first solved in a supercritical fluid (Fig. 1) [10].

Basic of this process is that substances can be solved in supercritical fluids and that solubility is satisfying.

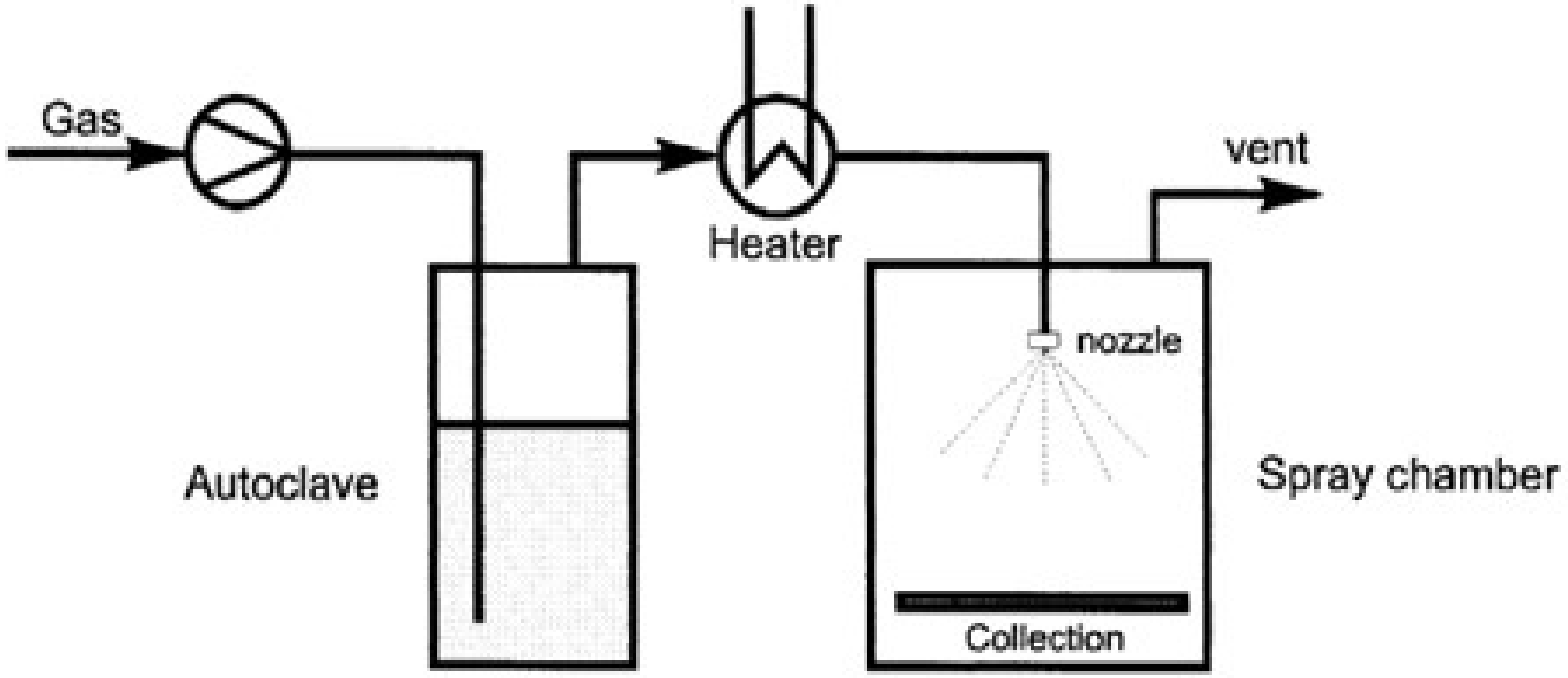



*Fig. 1. RESS process*

## *Gas antisolvent (GAS) process*

If the RESS process can not be used because of no or too low solubility in the compressed gas of material which has to be powdered, the Gas anti solvent process (GAS) is an alternative.

The advantage of this process is the lower pressure range and gas demand which has to be used and the easy separation of solid powder.

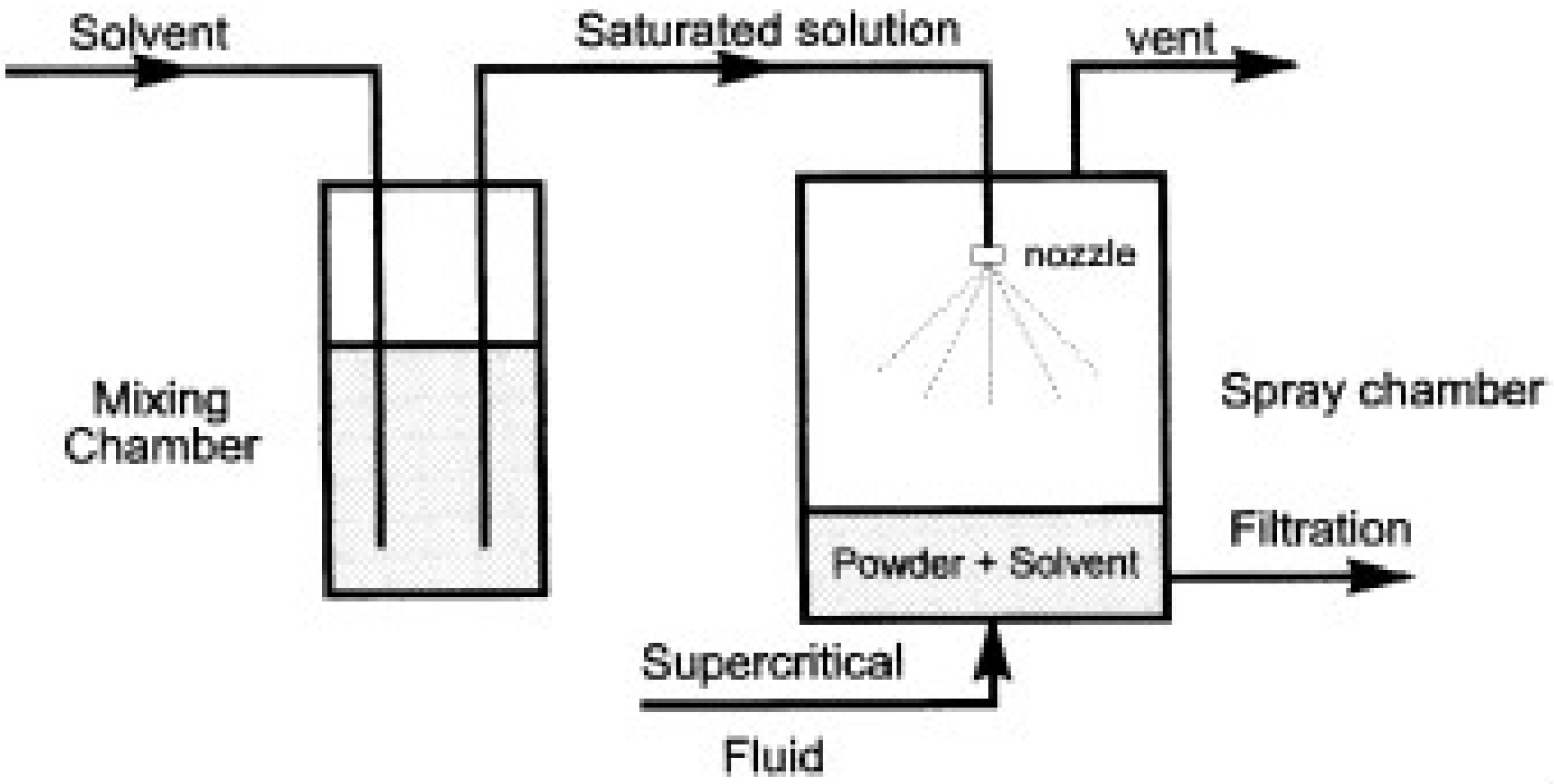



*Fig. 2. GAS process*

## *Supercritical antisolvent (SAS) process*

This technique is quite similar to GAS process with the only difference that the polymer, instead of dissolving in a gas, is dissolved in a liquid solvent and the resulting solution is sprayed in a chamber containing supercritical fluid as the antisolvent.

The advantage of SAS over GAS is that a rapid contact between the two mediums – antisolvent and the polymer solution.

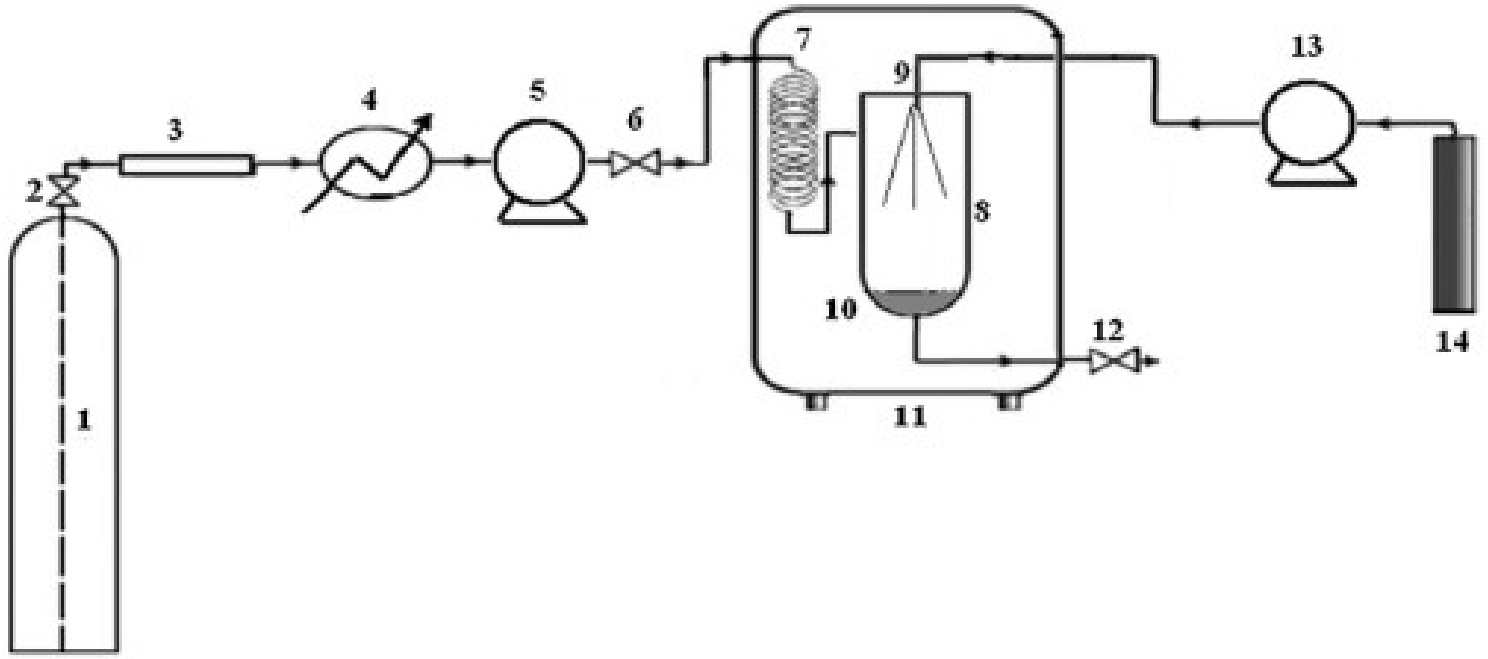



*Fig. 3. Experimental apparatus for micronization with SAS process: (1) CO2 cylinder, (2) valve on-off, (3) molecular sieve column, (4) cooler, (5) pump, (6) high pressure valve, (7) spiral heat exchanger, (8) precipitation vessel, (9) nozzle, (10) filter, (11) oven/water bath, (12) back pressure regulator, (13) feed pump, (14) feed tank*

# *Solution enhanced dispersion by supercritical (SEDS) process*

- SAS technique has been further upgraded into SEDS technique which is especially being used for single and binary compounds.

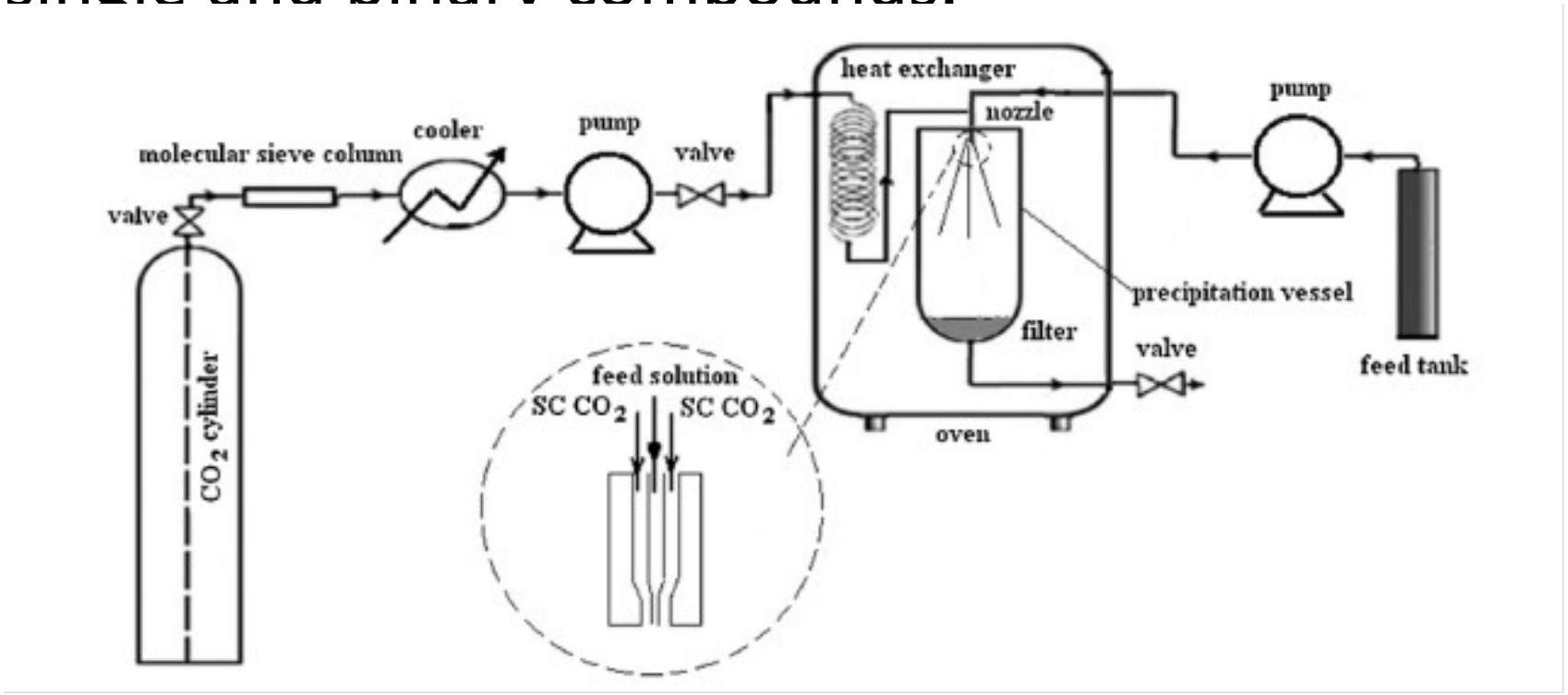


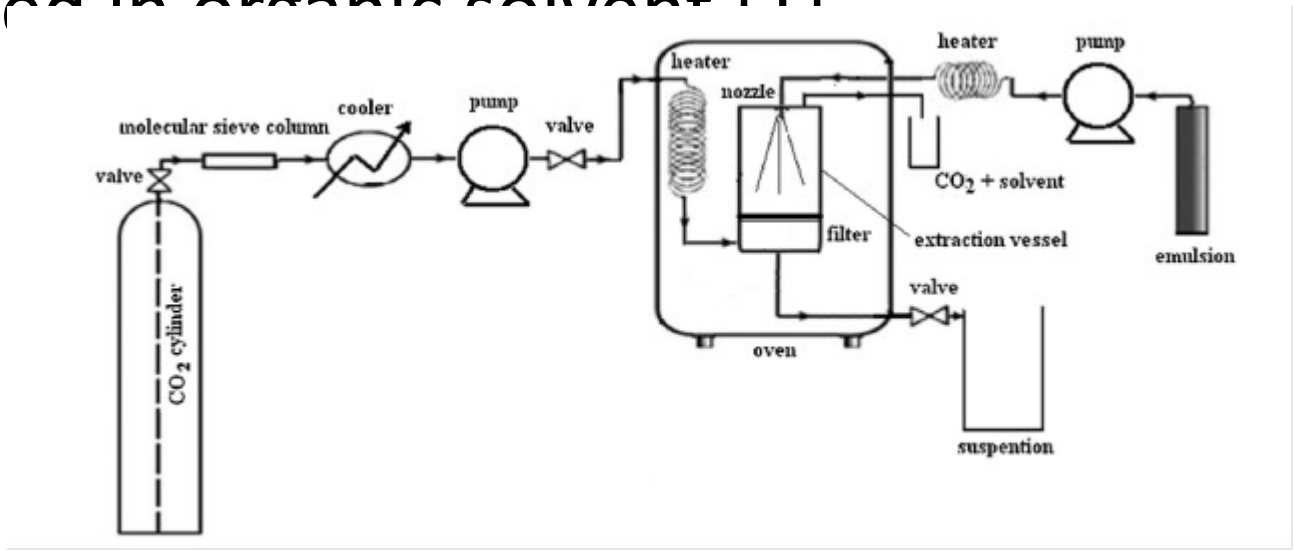

*Fig.4. Flow diagram of SEDS process*

***Aerosol solvent extraction system (ASES)***

The schematic diagram of the ASES process is the same as that of SEDS process [1].

***Supercritical fluid extraction of emulsion (SFEE)***

In continuous SFEE method (Fig. 5), a drug is dissolved in organic solvent [1]



- ***Particle from gas saturated solution (PGSS) process***

When scCO2 diffuses into the polymer, it lowers the melting point and decreases its viscosity. These characteristics are made use of in PGSS process.

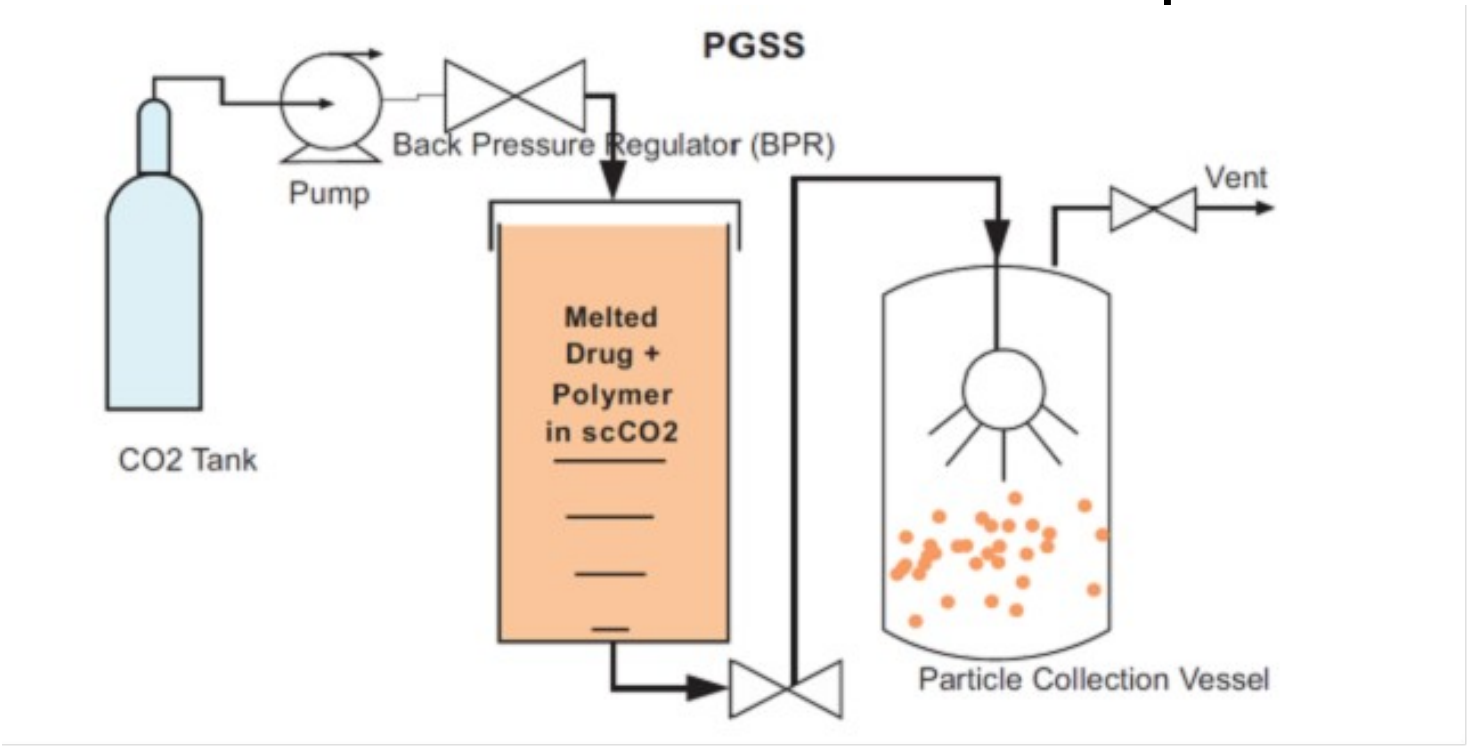



*Fig. 6. Schematic representation of equipment set up of PGSS process*

# CONCLUSION

- Supercritical fluids techniques are a good alternative for conventional methods for drug processing.
- The scCO2 is commonly used because it is nontoxic, nonflammable, and has low critical temperature and moderate pressure.
- The scCO2 micronization is a powerful way to improve the pharmaceutical solubility and bioavailability.

- As concerns the development of the SCF technology in the pharmaceutical industry, it is still in the early stages.
- Although particle generation processes using SCFs have been widely studied over the last decades, there are only a few industrial units.
- However, the technical developments seen in the SCF process over the last decade indicate that it may become a key technology in pharmaceutical industry in the future.