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# **RESS OR SAS: ELEMENTS OF CHOICE FOR FINE PARTICLE PRODUCTION**

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## **INTRODUCTION**

Supercritical fluid technology presents a new and interesting route for particle generation. Most of the drawbacks of the traditional routes, milling or liquid crystallisation, are avoided. Supercritical processes, RESS and SAS, give micro- or even nano-particles with narrow size distribution and can also be used to achieve micro-encapsulation or surface coating of an active substance particle with a polymer.

The bio-availability of pharmaceutical molecules depends on their absorption by the gastrointestinal tract which is governed by their dissolution rate. Micronisation techniques and especially those using SC-CO<sub>2</sub> which lead to an increase in the specific surface area (typically several tens of m<sup>2</sup>/g for a non-porous solid) can significantly contribute to this bio-availability improvement.

It is known that RESS is usable with CO<sub>2</sub>-soluble molecules while SAS can process non-soluble molecules. However, the choice is not so simple in reality. Very often, the solubility of pharmaceuticals is very low in pure CO<sub>2</sub> at moderate pressures (10 to 20 MPa) and temperatures (313 to 333 K). These operating conditions can be changed by the use of a co-solvent or by tuning the operating P or T. To know whether these possibilities exist or not, a good knowledge of the phase equilibria is required.

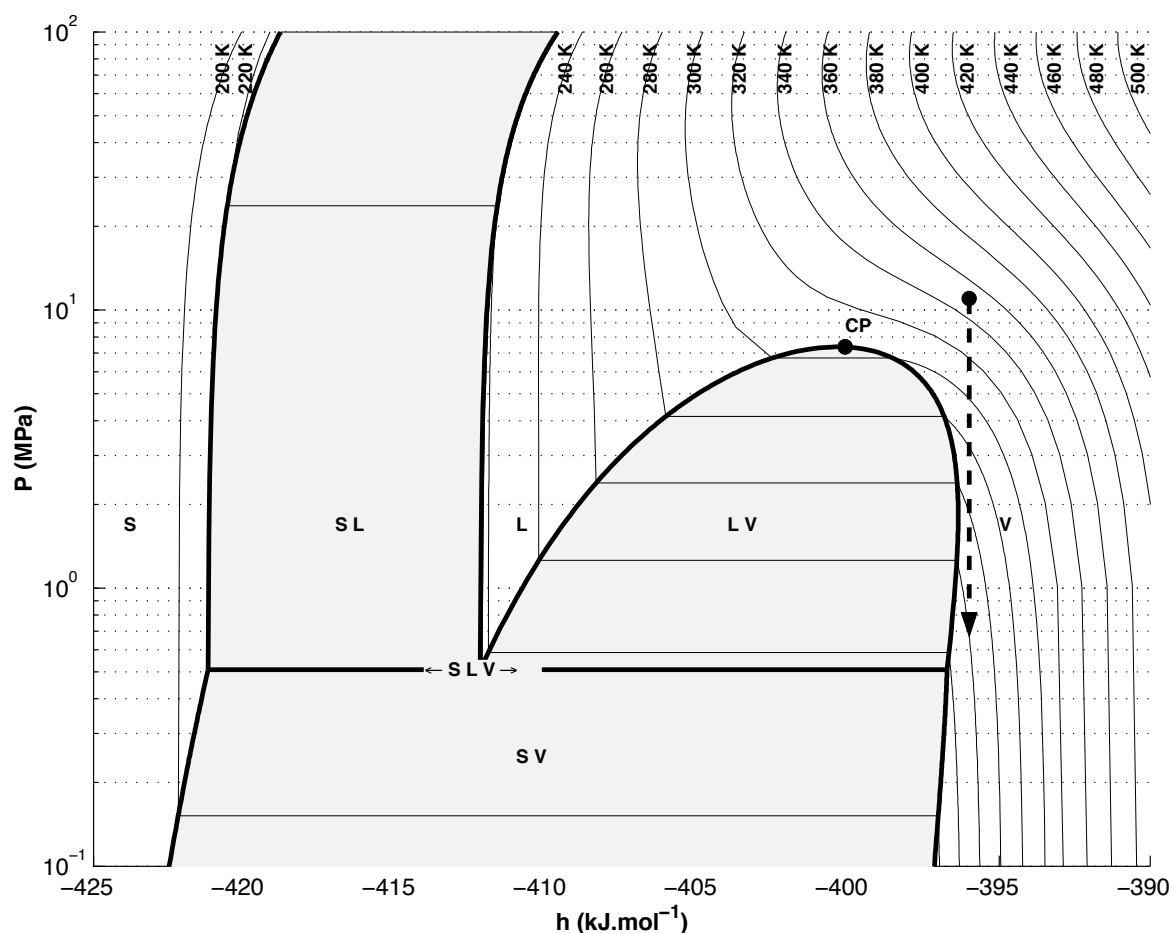
In this paper we will discuss how to determine the right strategy to be applied when facing such a problem and how to choose between a RESS or a SAS process.

## **OPTIMISATION OF THE RESS PROCESS**

RESS is a two-step process : after having solubilised a substance in a SCF, the mixture is suddenly depressurised in a nozzle causing fast nucleation and fine particle generation. In designing a RESS process, it is necessary to have the best possible understanding of what happens upstream from the nozzle that is to say during the extraction step. Therefore, it is important either to collect data from the literature when they exist, or to perform experiments or modelling, about the solute solubility in the SCF (1).

The key parameters of this extraction step are obviously the operating T and P. The flow rate of the fluid may also play an important role since a thermodynamic equilibrium may or may not be reached in the extraction autoclave. In fact, the kinetics of the dissolution must not be neglected and diffusional limitations can occur. Additional problems may be encountered when the solid to be extracted is not a pure component. Fractionation of the load can lead to a variation in the composition of the particles upon depressurisation.

To understand what will happen during fluid expansion, a Mollier diagram (pressure  $P$  vs. molar enthalpy  $h$ ) is very useful. An acceptable assumption is to consider that the depressurisation is an iso-enthalpic process (in fact, there is a variation of kinetic energy of the fluid, which should be taken into account). Therefore, the expansion step will be a vertical line (dashed arrow) on this diagram. Such a drop in pressure implies an important decrease in temperature as shown on figure 1 which is the Mollier diagram for pure  $\text{CO}_2$ .



**Figure 1. RESS expansion in the pressure-enthalpy diagram for pure  $\text{CO}_2$**

In the example shown on this figure, the starting point as well as the arrival point, are chosen to be in the single-phase zone of the diagram. However, to ensure such conditions, the temperature before expansion must be high (380 K in the example given), which may be incompatible with the solute to be extracted. A lower pre-expansion temperature may lead to a condensation or freezing of the SCF (the triple point of  $\text{CO}_2$  is at 0.52 MPa).

To compensate this drop in temperature and to avoid potential problem of clogging, a heated nozzle or a heating device just upstream from the nozzle can be used. The post-expansion pressure is also of the utmost importance.

Nucleation of the solute occurs during the sudden expansion of the solution and is due to the mechanical perturbation, which propagates at the speed of sound leading to very uniform conditions (2) and therefore to a very narrow particle size distribution.

Indeed, the expansion time depends not only on the speed of sound (which varies with the operating conditions and the nature of the fluid) but also on the length of the capillary nozzle.

However, an approximation between  $10^{-4}$  to  $10^{-6}$  second has been proposed. It is during this very short period of time that solubility falls by several orders of magnitude leading to large supersaturation ratios. The driving force of the nucleation process is the difference between the chemical potential of the solid in both phases (fluid and solid) which is related to the activity of the solute in the solution and at equilibrium. It is therefore the supersaturation which drives the nucleation. This supersaturation comes from the drop in density, which is very large especially near the critical point. The value of the enhancement factor (ratio of the solubility of a given solid in SCF over the theoretical solubility in an ideal gas) can be as high as  $10^5$  or  $10^6$ . These values give an idea of the large supersaturation ratios obtained, provided the fluid after expansion can be considered to be an ideal gas. This is the case when the expansion pressure is close to atmospheric pressure.

However, the expansion, may not be complete and can be controlled. It may be advantageous to limit the depressurisation and to let a pressure of a few MPa. This will diminish the supersaturation ratio but the recycling of the fluid might be facilitated. In fact relatively small changes in pressure may cause a dramatic fall in density and therefore in solubility. Again, the h,P diagram shown in fig.1 is of great help to determine which conditions can be used.

The most obvious drawback of RESS is the lack of solubility of several families of molecules in the CO<sub>2</sub>. To overcome this problem one way is to change the supercritical fluid. However, this is seldom possible since the few other candidate molecules (N<sub>2</sub>O, light hydrocarbons,...) are much more hazardous than is CO<sub>2</sub> (3).

To overcome this disadvantage, another possibility is to use the RESS process with a co-solvent being previously dissolved in the CO<sub>2</sub>. In this case the advantage of not using any chemical solvent is lost but it might be interesting to use a co-solvent using such low-toxicity solvents like acetone or ethanol.

The diagram h,P of the binary mixture is different from the pure component diagram. As an example, the diagram for the mixture (95 % CO<sub>2</sub> - 5% Ethanol) shows that the two-phase envelope is considerably enlarged by the addition of 5 % co-solvent (figure 2). This has to be taken into account when determining the operating conditions. The maximum mole fraction has to be determined to maintain a single phase fluid after depressurisation.

The choice of the proper co-solvent is not trivial and the affinity two-by-two supercritical fluid, co-solvent and solute are to be considered. A mixture of co-solvents may also be used. Moreover, it is not possible to predict the co-solvent effect from the solubility of the solute in the liquid co-solvent. Therefore, solubility measurements of the solid in the mixture SCF-co-solvent are highly recommended (4).

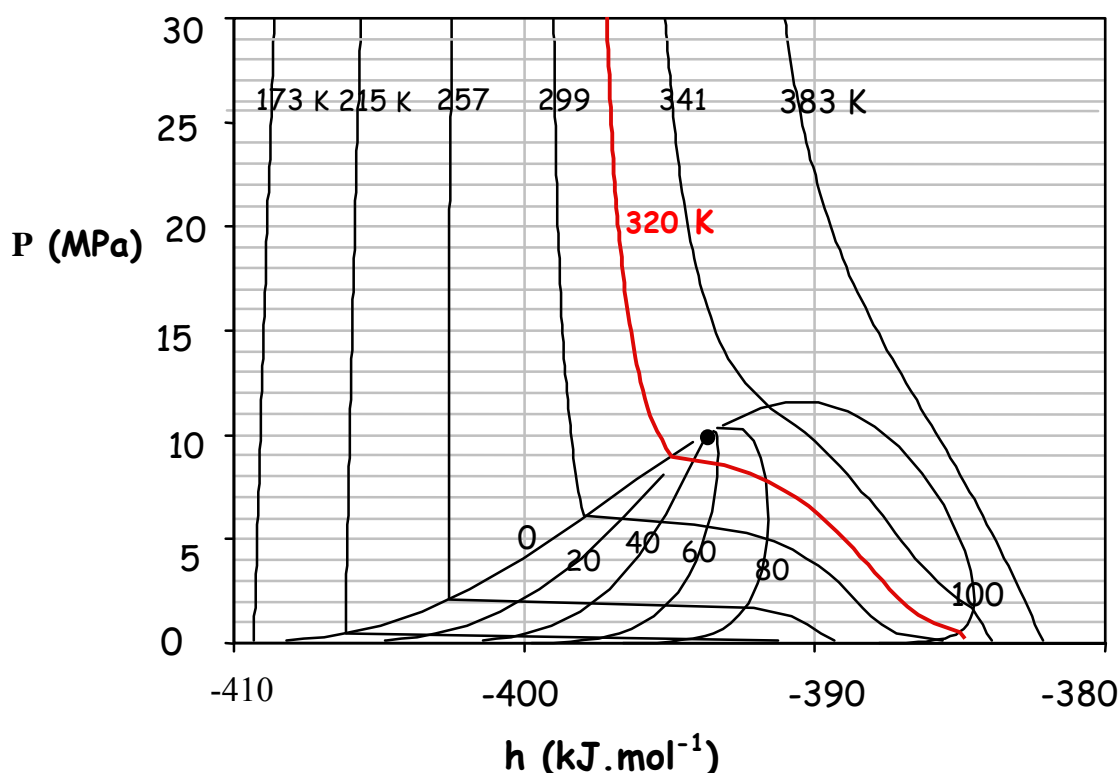
## **OPTIMISATION OF THE SAS PROCESS**

In the SAS process the substance to be micronised is dissolved in a solvent. The SCF acts as an anti-solvent that causes the crystallisation of the solute.

We will limit the discussion to semi-continuous process where solvent and anti-solvent are co-injected at the nozzle level. This process is sometimes referred as ASES or SEDS. Several parameters have an influence on the size and the morphology of the obtained particles. As with the RESS process the operating T and P upstream and downstream from the nozzle are obviously key-parameters. The role of the nozzle is to favour droplet formation which is rather different from the RESS case in which the main role of the nozzle is to provoke a huge drop in pressure. Nozzle geometry is also an important parameter in controlling the process. In

addition, the concentration of the solute in the solution and the relative flow rates of the solution and the anti-solvent are also to be taken into account.

The volumetric expansion of the organic solvent due to the dissolution of the anti-solvent has been recognised as an important parameter (5). The volume expansion can be predicted by using an equation of state with adequate mixing rules. Several authors have measured this expansion depending on the operating conditions and on the nature of the solvent. These data are of the utmost importance for the batch mode processes where the particle are produced from a liquid phase rich in solvent.



**Fig. 2. P,h diagram of a CO<sub>2</sub>-Ethanol mixture.** Mole fractions: CO<sub>2</sub>=95% and Ethanol=5%  
(Calculation : PR EOS)

For the semi-continuous mode, the expansion curves are less pertinent since the phenomena involved are rather different. The particles are formed from the drops of the solution which collide into the fluid phase. As the antisolvent flow rate is generally much higher than those of the solution, one can use the P,h diagram to see how many phases are present at the equilibrium.

On figure 2, the diagram of a 95 % CO<sub>2</sub>-5% Ethanol mixture, may correspond to a practical ratio of the anti-solvent over the solution of about 20. This diagram shows the two-phase L+V envelope which is to be avoided in order not to have a liquid phase in the expansion chamber. Such a liquid phase might re-solubilise the particles formed. In these semi-continuous processes which are those most studied today because of their potential industrial applications, the mass-transfer and nucleation occur at the surface of solution droplets in a continuous flow of antisolvent. It is therefore necessary to understand the fate of these droplets. There is a competition between two phenomena which occur simultaneously :

- the anti-solvent effect i.e. the dissolution of the anti-solvent into the solution. The consequence is the swelling of the solution droplets.
- the evaporation of the solvent into the anti-solvent. The consequence is the shrinking of the solution droplets.

A key-question must therefore be addressed : do the droplets of solvent in a flow of anti-solvent swell or shrink ? Shekunov *et al.* (6) showed results obtained with optical methods, image analysis, laser interferometry and PIV. They showed that droplets of ethanol in a turbulent flow of supercritical CO<sub>2</sub> do not swell as expected but on the contrary seem to retract as long as the ethanol dissolves ("evaporates") in the CO<sub>2</sub>. Depending on the pressure (below or above the critical mixture point) the behaviour of the droplet changes : at low pressures (below the mixture critical pressure) the droplets of ethanol decrease regularly. Nucleation and growth of crystals occur at the droplet interface leading to agglomerated particles. At higher pressures, a liquid ethanol jet appears from each droplet. Nucleation occurs within the shrinking ethanol-rich droplets and the mixing regime has a great importance. No swelling have been observed whatever the operating conditions.

Lora *et al.* (7) have recently given a simulation of a semi-continuous SAS with CO<sub>2</sub> as anti-solvent, toluene as the solvent and naphtalene and phenanthrene as solutes. They showed that three issues must be addressed : phase equilibria, hydrodynamics and mass transfer. Their calculations showed that the solvent droplets undergo a rapid swelling followed by a slower shrinking phase. CO<sub>2</sub> dissolution in the solvent and solvent evaporation into CO<sub>2</sub> increase with the CO<sub>2</sub> solubility in the solvent : toluene was compared with acetone and DMSO. Crystallisation of the two tested solutes varies : the anti-solvent effect is sufficient to provoke phenanthrene crystallisation while solvent evaporation is involved in naphtalene crystallisation. The variation of the flow rate ratio solvent/anti-solvent is therefore important for the latter solute while it is ineffective on the first solute.

Another study with the CO<sub>2</sub>-toluene system (without a third component to be crystallised) showed the dependence of droplet fate on the respective densities of the solvent and the anti-solvent (8). When the anti-solvent density is lower than that of the solvent - the most common case- the droplets can swell. However, they shrink in the opposite case. The extent of swelling (or shrinking) as well as the lifetime of the droplets are very sensitive to the operating conditions.

To optimise the production of particles from the droplets, and particularly when very fine particles are expected it is advantageous to work in the single-phase zone at high pressures where higher mass transfer and higher supersaturation ratios can be obtained. In this zone, the average lifetime of a droplet is short, implying rapid mass transfer, high supersaturation ratios and finally very small particles. The knowledge of the phase equilibria of the binary system solvent-antisolvent is compulsory before designing a semi-continuous SAS process.

## CONCLUSION

Supercritical-assisted particle formation has made a lot of progress in the recent years. Both RESS and SAS processes continue to undergo fundamental and applied research and have benefited from the recent years' advances. Several controversial issues still remain about : the influence of operating parameters on the characteristics of the particle produced (size, morphology, polymorphism), the comprehension of the fluid dynamics, the nucleation

phenomenon, the crystal growth under these specific conditions, the particle agglomeration in the jet, the method of scaling up, etc.

Because of its simplicity, RESS will remain the first process to be tested while the universality of SAS will ensure future developments for very different type of materials. Very often, semi-continuous SAS process and RESS process can compete for pre-industrial particle generation. A thorough study based on the phase equilibria and the solubility in pure CO<sub>2</sub> and in CO<sub>2</sub> + cosolvent within a broad range of T and P gives most of the required data for choosing the "right" process.

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