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GRAM TO KILOGRAM SCALE-UP OF SUPERCRITICAL ANTI-SOLVENT PROCESS

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Abstract:

Although very important R&D means are presently dedicated to applications of Supercritical Fluids (SCF) in the pharmaceutical industry, especially for formulation and particle design, few results were ever published on process scale-up. However, this step will be of particular importance in the future development of dense gas technologies. The scale-up of the Supercritical Anti-Solvent process was exemplified by processing a solution of a model molecule, *inulin*, in N-methylpyrrolidone with carbon dioxide as anti-solvent, at three different scales (from 1 to 10 and to 100). The particle size distribution, residual solvent content and recovery yield were compared, showing that scale-up is being mastered for elaboration of kg-level lots.

Introduction:

The Supercritical Fluid Technology is presently considered as a promising tool by the pharmaceutical industry for formulation and particle design [1-3], leading to tailor-made particles of chemical entities and bio-molecules. Moreover, the non-denaturing properties of supercritical carbon dioxide combined with its intrinsic sterility [4-6] are of particular interest for the stabilization and formulation of the coming therapeutic proteins.

Several processes were developed both for formulating water-insoluble (or poorly soluble) and hydrophilic molecules, including fragile bio-molecules, to come up to the pharmaceutical industry expectations. In particular, an important R&D work is on-going in the following domains : bio-molecules drying and stabilization, increasing bio-availability of poorly-soluble molecules, designing sustained-release formulations and preparing substances for drug delivery less invasive than parenteral (oral, pulmonary, transdermal) [7,8].

The Supercritical Anti-Solvent process (referred as SAS, ASES, PCA, or SEDS in literature), which uses the anti-solvent effect of supercritical CO_2 to precipitate the substrate(s) initially dissolved in a liquid solvent, is generally considered the more attractive for particle design because it permits to monitor the properties and composition of the particles with a great flexibility and for almost any kind of compounds [7,8]. As a result, this process was widely studied with hundreds molecules processed at lab-scale, but translating it at large scale still remains a challenge. Nevertheless, it is now necessary to show to the pharmaceutical industry that particles can be produced at industrial scale

while keeping their characteristics in order to make the technology more attractive than a simple lab tool.

Scale-up

Presently, so little is known on the particle generation mechanism that modeling remains quasi impossible and very few data have been yet published on SCF particle design scale-up. Thiering et al [9] discussed issues relating to scale up of anti-solvent precipitation but without giving concrete examples. Other teams successfully produced samples at different scales but batch sizes were still very limited [10,11]. On the economical point of view, two studies were proposed but the most recent one significantly underestimates the equipment cost and does not take the GMP extra-cost into consideration [12,13].
We will successively consider the different process steps: atomization, particle collection, residual solvent stripping from particles, particle recovery, and fluid recycling [14].

Atomization

In the SAS process, particle shape and size distribution is strongly dependent on the liquid solution injection device that influences the droplets size, coalescence and mass transfer between the two fluid phases. Conventional jet atomization processes are usually scaled up using some dimensionless numbers :

- $Re = \rho . U . \Phi / \mu$ (inertial force to friction force ratio)
- Weber number $We = \rho . U^2 . \Phi / \sigma$ (kinetic energy to capillary energy ratio)

where ρ is the specific gravity of the fluid, U the relative velocity of the two fluids, Φ the nozzle diameter, μ the viscosity of the fluid and σ the interfacial tension between the two phases. In recent publications, this general theory was applied to the pulverization of a liquid solvent into a SCF phase through a simple capillary nozzle [15] or a coaxial nozzle [16,17]. Correlation between particle size distribution and both numbers was demonstrated [16,17], while the ratio $(We)^{0.5}/Re$ was proposed by Czerwonatis et al [15] to describe the zone where a free liquid jet is atomized into the fluid. The easiest way to scale-up would be to keep all the parameters constant and replace one nozzle by several similar nozzles. However, from a practical point-of view, it seems difficult to achieve pulverization through several nozzles with exactly the same pressure drop and fluid velocity. So, for this study, we decided to increase the nozzle diameter at each step while keeping the liquid velocity constant.
Another parameter that can strongly modify the morphology of the particles is the post nucleation growth inside the collection chamber [8]. So, it is recommended to keep all parameters constant (fluid/substrate ratio, temperature and pressure) and especially the residence time before particle recovery.

Particle collection

Collection of micronic and submicronic particles is a complex operation and bag-filtration is generally preferred. In the present study, on the small-scale equipment, we used a filter paper supported by a sintered disk at the bottom of the precipitation vessel whereas a bag filter made of PTFE-coated woven fabric is preferred on the large equipment. However, improvement of this system is still necessary to prevent particle re-agglomeration, particularly when submicronic particles are generated; at large-scale, we would recommend a two-step process where precipitation and collection would take place

in two different vessels in order to be able to control the different parameters of these two operations separately [14].

Residual solvent stripping from the particles

Another major issue is related to the elimination of residual solvent adsorbed onto the formed particles. In the rare publications dealing with stripping conditions and efficiency, and according to our own experience, it appears that huge fluid/substrate ratios are required, often higher than those used for the atomization itself. Moreover, we think that this method cannot be directly applied at large-scale because fluid percolation through the particle layer collected onto the filter is not satisfactory due to fluid bypass. However, in the present study, as there was no need for reaching very low residual solvent levels, we stripped the powder collected onto the bag filter prior to recovery in all cases.

Fluid purification and recycle

At large scale, the supercritical fluid must be recycled as large amounts of fluid are needed to achieve particle formation with an acceptable residual solvent content. This is a major issue as the classical liquid-fluid separators currently used in Supercritical Fluid Extraction cannot achieve complete solvent removal from the fluid prior to recycle [14].
In this study, the fluid was recycled during the pulverization step and the first part of the stripping step. During the second part of the stripping step, the particles are flushed with make-up carbon dioxide in order to extract the final solvent content and prevent solvent condensation during system decompression.

Scale-up results

For several years, the R&D and the equipment construction teams of Separex have been working to design equipment adapted to operate various SCF particle design processes at different scales in compliance with the rules enforced in the pharmaceutical industry (GMP). For this study, four units were used:

- A small-scale system (X0.1) with a 10 mL precipitation chamber and a CO_2 flow rate up to 0.5 kg/h;
- A lab-scale pilot plant (X1, figure 1) with a precipitation vessel of 0.5 L and a CO_2 flow rate up to 5 kg/hour;
- A larger equipment (X10, figure 2) with a precipitation vessel of 4 L and CO_2 flow rate up to 20 kg/hour;
- A commercial scale pilot plant (X100, figure 3) with a precipitation vessel of 50 L and CO_2 flow rate up to 500 kg/hour.

In order to demonstrate that scale up can be performed form lab to commercial-scale, a model molecule was pulverized by the anti-solvent process. *Inulin*, a polysaccharide extracted from chicory root, was dissolved in N-methylpyrrolidone (NMP) and the solution was pulverized in supercritical CO_2 at 20 MPa and 40°C. Although concentrated solutions of inulin in NMP are very viscous, we succeeded in pumping this solution with up to 300 g/L of solute. The inulin solution and the supercritical fluid were co-introduced into a mixing chamber before atomization in order to improve jet break-up.
After feasibility tests at lab-scale (X0.1), samples were prepared on the three plants: 2 g on X1, 20g on X10 and 200 g on X100. The supercritical fluid flow rate and nozzle parameters were increased in order to keep the fluid velocity and the mixing volume

constant. The duration of the residual solvent stripping step was the same for the three scales so as to achieve the same residence time in the atomization vessel for all samples.

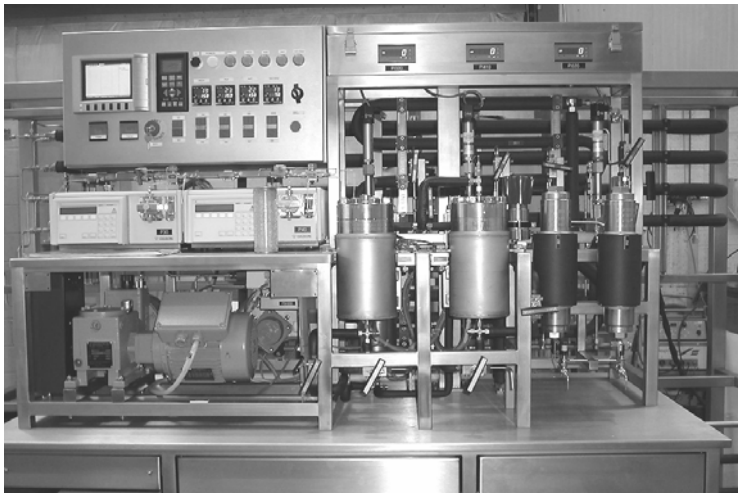


Figure 1 : Pilot-scale equipment (X1)
CO_2 flow rate : 5 kg/h - Atomization vessel : 0.5 liter

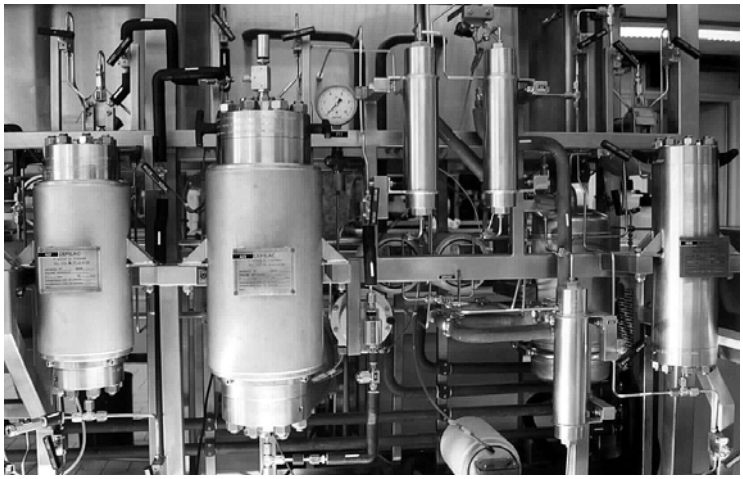


Figure 2 : GMP pilot-plant (X10)
CO_2 flow rate : 20 kg/h - Atomization vessel : 4 liter

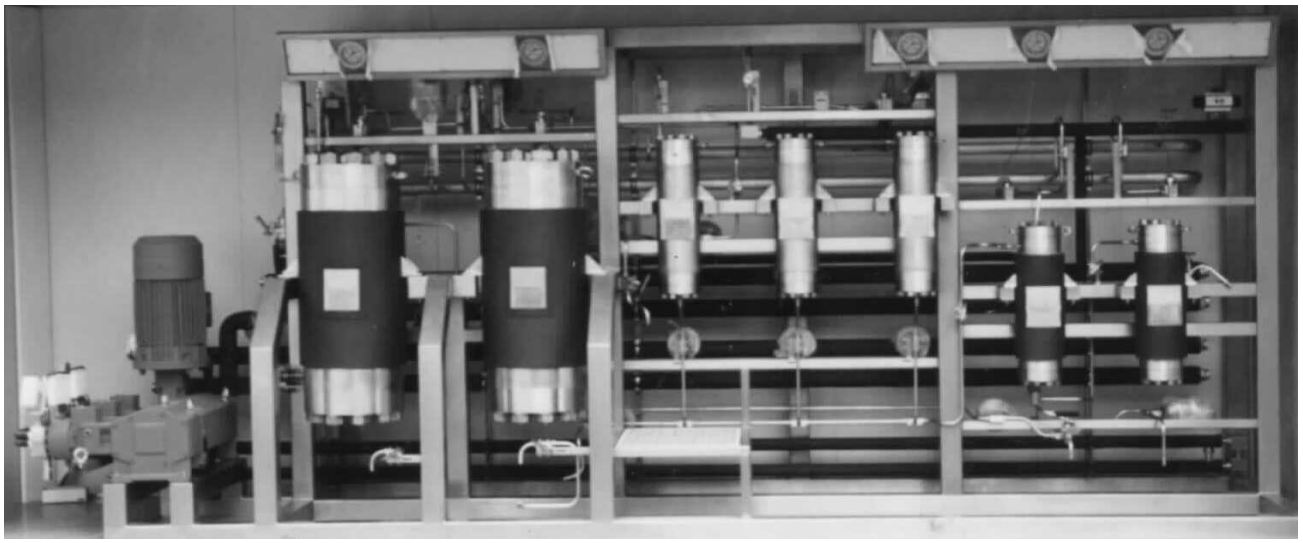
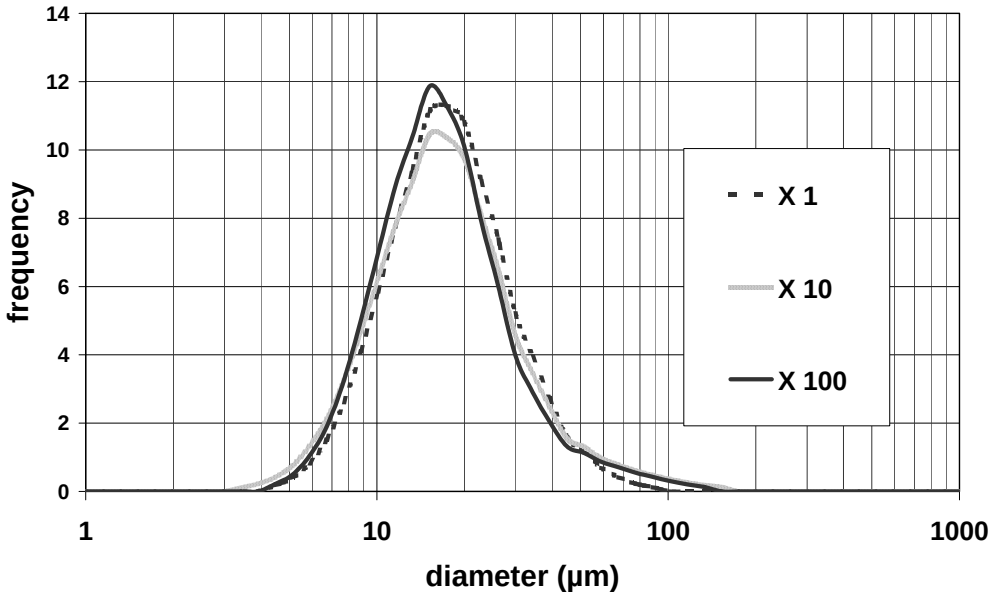


Figure 3 : SCF plant (X100) CO_2 flow rate : 500 kg/h - Atomization vessel : 50 liter

As shown on figure 4, the particle size distributions of the samples generated at the three scales are strictly identical, in the range wished to obtain a "non-dusty" powder. Moreover, the particle recovery yield is increasing with the scale: from 61% for X1 to 97% for X100 while residual solvent content is varying between 3 to 5%. It is to be noticed that the decrease of the residual solvent concentration is very slow, even with very high solvent ratios, as most of the solvent probably bypass the powder; so, we would rather recommend to re-process the powder in a classical Supercritical Fluid extraction equipment if a lower concentration is required.

Figure 4: *Particle size distribution of Inulin particles prepared by ASES process on various scale plants : X 1 (2 g sample), X 10 (20 g samples), X 100 (200 g sample)*



It is to remarkable that a very low fluid-to-substance ratio could be achieved (~50 kg/kg), much lower than generally stated in most publications (500 to 10,000), leading to a more acceptable process from an economical point-of-view [7,8].

Conclusion and further work

The results obtained with inulin, pulverized from a NMP solution using the Supercritical Anti-Solvent process at three different scales (0.5L, 4L and 50L), showed the same particle size distribution and similar residual solvent contents while recovery yield increases with scale. Moreover, further experiments realized on the three different scales with a slightly different proprietary molecule confirmed these results, except that much larger lots, up to 2 kg, could be prepared on the X100 equipment.
Although this work is a preliminary step, particularly since several critical points (particle collection, residual solvent stripping and fluid recycling) are yet to be improved, commercial scale production of particles by SAS is presently available.

Extended work is now on-going with two major objectives: translating the inulin precipitation on a 500 L-unit and preparing smaller-size (inhalation range) particles of therapeutic molecules at large scale (X100).

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