

# **Scale-up Issues for Supercritical Fluid Processing in compliance with GMP**

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## **I. SCOPE**

Meanwhile very important R&D means are dedicated to applications of Supercritical Fluids (SCFs) in the pharmaceutical industry, a very limited number of commercial plants are now operating or under construction, and few companies have acquired some know-how in process scale-up, especially in SCF formulation and particle design, in compliance with the constraints imposed in this industry (traceability and GMP, sterility,...).

In this chapter based on our experience gathered when building tens of SCF plants during the past decade, including some for processing clinical lots in compliance with GMP, we will try to present both the general scale-up rules applicable to large-scale SCF plant construction, operation and maintenance, and the specific scale-up know-how related to pharmaceutical plants, and especially those dedicated to drug formulation and particle design.

## **II. SCF PROCESSES IN THE PHARMACEUTICAL INDUSTRY**

Many Supercritical fluid (SCF) processes are now under development in various industries [1-12], including many *pharmaceutical* applications [13] :

- Supercritical Fluid *Extraction* (SFE), *Fractionation* (SFF) and *Chromatography* (SFC), for extraction and purification of active substances ;
- Supercritical Fluids as *reaction media* for selective synthesis of active ingredients [6,8,14-16] ;
- Supercritical Fluid *drug formulation* by manufacturing *innovative* therapeutic particles, either of pure active compounds or composites of excipient and active compounds [17,18].

In fact, very few compounds can be used as SCFs for most applications at commercial scale (see table 1). *Carbon dioxide* is by far the most attractive SCF for many reasons : Inexpensive and abundant at high purity (food grade) worldwide, it is not flammable, not toxic and environment-friendly ; moreover, its critical temperature (31°C) permits operations at near-ambient temperature that avoids product alteration, and its critical pressure (74 bar) leads to “ acceptable ” operation pressure, generally between 100 and 350 bar. In fact, supercritical carbon dioxide behaves as a rather weak “non-polar” solvent, but its solvent power and polarity can be significantly increased by adding a polar co-solvent that is chosen among alcohols, esters or ketones. *Ethanol* is often preferred as it is not environment-hazardous, not very toxic and available pure at low cost. *HydroFluoroCarbons* (HFC) are very costly and their specific properties rarely justify their use in replacement of carbon dioxide.

Although they do not present the advantages of carbon dioxide, other fluids are also considered for industrial applications in spite of their flammability and related explosion hazards :

- *Light hydrocarbons*, especially liquefied *propane*, that appears to be a much stronger solvent than carbon dioxide vis-à-vis lipids ;

➤ *Dimethyl ether*, used as liquefied gas, that behaves as a “polar” solvent able to dissolve a very wide range of compounds including many polymers [19].

It is also important to notice that SCFs have biocide properties against most microorganisms (fungi, bacteria, viruses) [20-25], and, even if it cannot be considered as a real sterilizing agent, SCF processes are intrinsically sterile and never increase the bio-burden.

### **III. BASIC RULES FOR SCF PROCESS SCALE-UP IN COMPLIANCE WITH GMP**

Prior to dealing with the specific scale-up issues related to SCF extraction/fractionation and SCF drug formulation plants, we will present the basic background used to build and operate any SCF equipment in compliance with GMP, and firstly the safety rules [26] that must be imposed in any case.

#### **A) Safety in Supercritical Fluid operations**

As handling supercritical fluids and liquefied gases presents important hazards, safety must be taken into account at any step of equipment design, building, installation, operation and maintenance, and a detailed analysis of potential hazards should be conducted for any case.

##### **1. Mechanical hazards**

Both design standards and official tests that are enforced by state agencies, in combination with strict inspection procedures, limit this hazard to quasi-zero, especially on large-scale units. No need to say that equipment shall *never* be modified without enforcing the same standards and obtaining the manufacturer consent. But, some issues are often underestimated, especially on R&D multipurpose equipment :

- Plugging : Most solid-fluid equipment use baskets closed by filter disks ; on large scale units, plugging causes disk rupture but, on small-scale equipment, the disk may

not break on depressurization and compressed CO<sub>2</sub> remain in the basket that may be brutally ejected and/or explode. So, we strongly recommend to be extremely prudent when processing material that could lead to plugging, foaming or expanding (polymers, "sticking" materials, highly viscous extracts, etc.) and to open valves on autoclave top *and* bottom.

- Tubing connection rupture : Double-ring connections, commonly used on most small-scale equipment, are safe and reliable when the screwing procedure is strictly followed. Otherwise, the rings may slip on pressurization. We recommend to always verify the good sealing of the rings, and not to use double-ring fittings on tubings larger than ¼" and/or for pressures over 300 bar, for which secure high-pressure screwed connections should be preferred.

- Metal fatigue and fragilization : Large-scale pressure vessels are commonly built in carbon steel covered by an internal stainless steel cladding. The life duration of high pressure vessels is linked to the number of pressurization / depressurization cycles, commonly 10 000 to 20 000 cycles, depending on their design – that must include a fatigue calculation - and any operation shall be stopped when the limit number is reached. Moreover, carbon steel may be subject to phase transition and become brittle when temperature decreases below -20°C. As adiabatic CO<sub>2</sub> depressurization leads to very low temperatures, a hot fluid circulation in the autoclave jacket and a "controlled" depressurization rate are required. Another hazard might also appear in case of perforation of this cladding as CO<sub>2</sub> (in presence of water) may corrode the carbon steel; so, a strict inspection must be made frequently to detect any cladding damage.

## **2. Thermodynamic hazards**

- Dry ice : CO<sub>2</sub> handling often leads to drastic temperature decrease and plugging of filters and tubings by solidified water, products or dry ice itself. This plugging might be

dangerous when occurring in basket sintered disks, captors tubing, or vent line that must be always “over-dimensioned” and built carefully.

- B.L.E.V.E. : The "Boiling Liquid Expanding Vapor Explosion" characterizes the physical explosion of a liquefied gas/supercritical fluid that is brutally depressurized to atmosphere, in case of pressure vessel rupture or opening. In fact, this hazard is almost only to be feared in case of metal weakening cause by a intense fire around the vessel(s). It is the reason why it is recommended to install fire detectors that could order immediate depressurization of the whole plant in case of fire.

### **3. Chemical hazards**

- Flammable fluids, co-solvents, products : Explosion-proof equipment, buildings and procedures must be enforced when flammable fluids are handled, especially light hydrocarbons and dimethyl ether. Explosive atmosphere sensors have to be connected to high-power fans and to fluid reservoirs stop-valves. N<sub>2</sub>O must be avoided for processing flammable products, as it may behave as a comburant and lead to explosion.

- Corrosion : This hazard must be evaluated prior to processing any material. Supercritical water oxidation leads to extreme corrosion rates and special alloys are required.

### **4. Biological hazards**

- Asphyxia : CO<sub>2</sub> build-up in closed rooms could lead to people asphyxia. It is the reason why all possible CO<sub>2</sub> emissions must be collected into an "over-dimensioned" vent line ensuring a good dispersion of the gas in the outside atmosphere. Moreover, it is highly recommended to install CO<sub>2</sub> detectors in the equipment room, but also in any connected room (especially underground passages and cellars, where CO<sub>2</sub> that is heavier than air may accumulate) for action on high power fans and information of operators.

- Chemical and biochemical toxicity : Handling any co-solvent or raw material or fluid that presents a danger in terms of chemical or biological hazard must lead to drastic care as supercritical fluid equipment work at high pressure with possible leaks at any moment. Fluid leakage often leads to aerosol formation that may be easily inhaled. In particularly dangerous cases, it is necessary to isolate the equipment in a closed room or box (figure 1) with remote control, meanwhile environment must also be protected by effluent treatment.

## **5. Safe operation**

We would stress on the fact that a key for a safe and reliable operation of a supercritical fluid equipment consists of a *very cautious training of the operators*. Moreover, automation is required with a high degree of *redundancy* taking into account all potential issues (fire, electrical power or instrument air failure, computer or instrument problems, etc.).

### **B) Large-scale SCF plants design and operation**

Basic chemical engineering for supercritical fluid equipment design can be found in a recent book by Brunner [10], but few data are presently available for calculation of main parts to be assembled into large scale SCF plants. Moreover, special issues related to GMP compliance are to be taken into account at all steps of design, construction, operation and maintenance.

#### **1. General layout**

In order to avoid contamination of the processed products, it is generally required to install the vessel(s) that have to be filled and emptied in contact with atmosphere in a “clean” room, the class of which depending on the type of drug and, in certain cases, sterility is demanded. As a SCF unit is complex and includes various equipment that can generate or accumulate dust and other potential pollutants, we obviously recommend to split the plant

in several rooms and isolate the vessel(s) into and from which the product is transferred, in a clean room meanwhile the other pieces of equipment are located outside this clean room. As very often a flammable fluid or organic solvent, or potentially explosive dusts are handled, large-scale plants must be built under the explosible atmosphere standards; in this case, the utility services shall be located outside the explosion-proof area and all the automation system in a remote control room. Of course, workers and environment protections are imposed in all rooms where the process fluids are handled as a leak may happen and release active substances.

## **2. Automation**

All large-scale units are designed with a complete automation permitting an easy documentation of all what is done during the plant life : Cleaning, production, maintenance, with edition of the detailed run journals and record of all processed substances, all incidents and plant modifications. This is a basic requirement for complying with both safety standards and GMP.

## **3. Heat exchangers**

Double-tube counter-current heat exchangers are currently used on pilot and semi-industrial plants, but when the fluid flow rate exceeds  $500 \text{ kg}\cdot\text{h}^{-1}$ , shell-and-tube exchangers are required for providing a sufficient transfer area. According to our experience, we recommend :

- Process fluid always on tube side and heating/cooling medium on shell-side ;
- Horizontal SCF heater (when the liquefied fluid is pumped) or cooler (when the fluid is compressed in gas phase), with one pass on shell-side and two passes on tube side, U-tubes being acceptable ;

- Vertical reheater(s) downward fluid decompression between the high pressure operation and the separators with one pass on tube side for downward high speed flow of process fluid in order to avoid extract deposition and plugging ;
- Vertical condenser (when required to liquefy the fluid prior to recycling by pumping) with one pass on tube-side and downward flow of process fluid so as to avoid plugging by extract entrained from the separators.

The designer must also pay attention to the insulation materials used on tubings connected to heat exchangers and utility services inside the clean room as these materials may accumulate and/or release dust and may be difficult to clean. This is especially difficult to solve for small-scale equipment meanwhile classical solutions using metal envelops are available for large-scale pipings.

#### **4. Autoclaves**

Most attention is paid to closure systems permitting a fast and easy opening/closure, as all solid processing is realized in batch mode and requires a great number of repetitive operations to fill and to withdraw the baskets containing the raw materials. First of all, these closure systems must be very safe and reliable so as to avoid any risk of moving them when the autoclave is pressurized. Generally, a redundancy is proposed through automation and an additional passive system blocking the closure when some pressure remains inside the autoclave. Clamp-closure systems are often preferred as they are very safe and easy to move automatically (Figure 1). The remark about insulation materials presented at the precedent paragraph also apply to thermal insulation of all vessels located in the clean room.

#### **5. Separators**

Most SCF plants have separators designed as large empty gravity settlers, but significant savings can be made by using much smaller-volume cyclonic chambers that are of special interest when the density difference between the extract and the fluid is low. In the case



where the substrate is very volatile and significantly soluble in the fluid at the separation stage or present at trace concentration, sorption onto an adsorbent bed is required to either purify the fluid prior to recycle (for example when pesticides are removed from a raw material) or to recover a valuable fraction of the extract that should have been lost otherwise (like light ends of flavors or fragrances) ; granular activated carbon is often preferred as it is inexpensive and has a very large sorption capacity (~1 g/g) and collection efficiency meanwhile it can be easily desorbed by the fluid itself at SCF conditions. For similar applications, distillation of the liquefied fluid has also been proposed. In most cases, it is also valuable to filter the fluid prior to recycle in order to avoid entrainment of raw material or extract fine particles that may accumulate and plug inside the condenser or downward pipings and capacities, resulting in losses of heat transfer efficiency, and finally requiring to stop the plant for a difficult-to-operate cleaning.

## **6. Fluid management**

The purity of the fluid contacted with the substrate is obviously a key-parameter for preserving the final product from any contaminant. So, great attention must be paid to the fluid supply and delivery to the plant and to the fluid recycle with potential build-up of trace contaminants.

### ***6.1 Fluid supply, storage and delivery***

In fact, carbon dioxide is available at high purity (generally 99.5 % at least) and most impurities are not at all harmful (mainly moisture, and very low concentrations of nitrogen, oxygen, methane and light hydrocarbons). However, non-volatile organic pollutants must be detected and evaluated prior to use the fluid in a pharmaceutical application as this may indicate contamination with lubricants during the manufacture process, although presence of harmful polycyclic aromatic hydrocarbons is highly improbable. For a plant operating in

compliance with GMP, traceability shall be required from the fluid supplier, with systematic analysis of each lot delivered to the storage.

The storage, consisting in a cryogenic vessel (capacity varying from 4 to 10 tons) where carbon dioxide is stored in liquid state at about 1.8 MPa, may be a source of contamination if not properly designed, cleaned and operated. Stainless steel tanks are preferred to the classical carbon steel vessels as CO<sub>2</sub> induces the formation of rust in presence of moisture, and filtering submicronic rust particles from liquid CO<sub>2</sub> is not easily feasible.

But the most important potential source of contamination is the pump or compressor required to pump the liquefied CO<sub>2</sub> to the plant : A non-lubricated pump must be used instead of lubricated volumetric compressors. Moreover, it is strongly recommended to design the compressor system and the delivery line so that no contamination could occur from any other plant and no reverse flow could happen from the plant towards the storage. As the operating pressure inside the plant is generally far over the pressure in the storage, experience shows that such reverse flow is not easy to avoid when problems happen during plant operation (one-way valve or compressor check-valve leakage, control system failure, etc.). The complete purge and validated cleaning of the storage and delivery line shall be operated between the processing of different products to avoid any risk of cross-contamination.

## **6.2 *Fluid recycle***

In all large-scale plants, the fluid is recycled for obvious economical and ecological reasons. This means that the separation of solute(s) from the fluid prior to its recycling must be as perfect as possible to avoid deposition throughout the recycle loop, especially onto the colder parts (condenser, sub-cooler, liquefied gas reservoir), that may lead to plugging and stop the unit for a long time. Moreover, some problems, unknown at lab or pilot-scale, may

appear as some tiny impurities may accumulate in the fluid phase (water, inert gases, pollutants, etc.). Two fluid cycles can be used :

- Liquefied gas pumping : Membrane pumps are preferred for flow rates up to 1,000 kg/h meanwhile piston-plunger pumps are used for larger capacities. It is important to notice that pump check-valves presents a significant pressure drop requiring a sub-cooling of the liquefied gas of at least 3°C below the boiling temperature at the inlet pressure (~40 to 50 bar for carbon dioxide) to avoid cavitation in the pump head that must also be cooled. However, some processes require very large fluid flow rates (> 1,000 kg/h), under a small pressure drop, that are delivered by centrifugal pumps.

- Gas compression : It is also possible to compress the gas through a compressor. However, these equipments are generally considered as more expensive than pumps and more costly in maintenance, although savings can be made as no refrigeration machine and condenser are required. Moreover, some problems may occur if heavy or waxy materials are entrained in the gas phase to the compressor.

Regarding compliance to GMP, the main issue is related to avoid trace-contaminant build-up in the recycle loop. In fact, this risk is rather limited as the make-up flow rate for replacing the fluid consumption is generally higher than 10% of the recycle flow rate. However, a periodic check and complete venting of the installation is necessary.

### ***6.3 Fluid disposal***

When active substances are processed, no direct fluid disposal is acceptable and the depressurized gas can be vented to atmosphere only after treatment. In most cases, the active substance that may be carried out by the gaseous effluent is solid and filtering is efficient. In rare cases, when the active may be present in form of an aerosol, water scrubbing is required. It is to be noticed that the vent line is a basic tool of safety and in no case effluent venting in emergency shall be hindered. It is the reason why any effluent

treatment unit must be designed for emergency release flow rate, and can be bypassed in case of plugging.

## **7. Construction constraints**

SCF equipment must comply with both high-pressure standards and pharmaceutical standards. This is generally not possible to satisfy both demands, although it is not easy to find high-pressure pieces compatible with the Clean-In-Place (CIP) and electro-polished internal surfaces (for thick-wall tubings) requirements. All kind of threads on the fittings, on the connections and on the vessel opening system should be avoided when possible because of the cleaning difficulties. When CIP is not possible, all parts must be designed so that they could be dismantled quickly. Moreover, it is frequent that some minor pieces in contact with the process fluids have to be changed to avoid potential contamination ; similarly, all lubricants present on valve stems must be replaced by pharma-accepted ones. Obviously, the major attention must be paid to ease further cleaning : All welds should be smooth (orbital welding is required for all tubing assembly) and dead-volumes minimized. Moreover, it is extremely important to design the whole pipe-works so that a *total* drainage can be easily operated during the cleaning phases. Cleaning validation is a key issue of the design and remains a high time consuming operation. A careful design of any tube, vessel and piece of fitting is essential, and must be done so that all the necessary clean checks are possible when imposed by the validation method. Straight pipes, no dead volume fittings, access to any internal parts of the equipment need to be checked during design reviews.

## **8. Operation of large-scale units**

Large-scale SCF units are operated with the same rules as other pharmaceutical plants according to a validated plan (Standard Operation Procedures) with the help of the control system. We would just draw the attention to some specific issues :

### ***8.1 Solid processing***

According to our experience, many issues may happen along long-term exploitation :

- Fine particles may cause basket filter disk deformation ; this is the most widely encountered problem as most operators do not take enough care to the raw material particle size distribution during grinding. We strongly recommend to avoid very fine particles by grinding control and/or screening the raw material prior to filling the baskets ; a paper filter may be an aid to prevent this problem. In other cases, the raw material may agglomerate in form of a thick “cake”, what drastically reduces the fluid-material contact and extraction efficiency and possibly leads to total plugging and deformation of the sintered disks. It is preferable to prepare pellets with such “sticking” materials or when this is not possible, we recommend to blend the raw material powder with an inert granular or fibrous (cellulosic for example) material that will prevent agglomeration. In the worst case, disk plugging may lead to basket deformation and blockage inside the extraction autoclave, with resulting damage to the autoclave wall during withdrawal ; this may be avoided by controlling the pressure drop between the inlet and the outlet of the vessel below the value that irreversibly damages the basket and/or the sintered disks.
- Basket deformation may happen due to shocks during handling, and autoclave wall damage may be caused by shock with the basket bottom during introduction : this may lead to a drastic loss of efficiency of the extraction due to fluid by-pass between the basket and autoclave walls when the external gasket of the basket is not totally

sealing. So, it is important to operate with adequate means of basket handling and careful manpower.

### **8.2 Liquid processing**

Liquid processing is much easier to operate as pressure vessels are not often opened and closed. However, tubings or column packing plugging may happen : It is generally a slow process with deposition of a solid or highly viscous material, that progressively reduces the open section and creates zones no longer swept by the fluid, what generally “catalyses” the deposition, until the moment where the operation shall be stopped for cleaning. This phenomenon is not easy to detect and to prevent, as, in most cases, it does not appear at pilot-scale where experiments are generally conducted during short periods. To avoid this, it may be necessary to pre-treat the liquid(s) (filtration, etc.), to change the operating conditions (possibly increased temperature) or to operate preventative column cleaning regularly.

## **9. Maintenance of large-scale units**

Industrial production with supercritical fluids requires a high reliability with drastic safety requirements : This requires a *preventative* maintenance as many parts must be inspected and some changed periodically ; moreover, a rigorous operation plan must be enforced to eliminate any risk of deterioration of the basic parts, and safety sensors must be continuously logged. This firstly concern the high-pressure pump(s) (check-valves and membrane(s) are highly sensitive to abrasion or perforation by solids), autoclave closure systems and gaskets (to prevent fluid leakage) and baskets (external gaskets to avoid solvent by-pass ; filter disks plugging to avoid deformation or rupture). Of course, pressure vessels must be inspected and submitted to pressure tests according to official standards. Moreover, the main process valves must be often checked, as they are the key of safe operation during autoclave opening for raw material change. Sensors must be recalibrated

periodically, in comparison with traceable reference sensors, and data logging validated. Finally, we would stress on the fact that maintenance is greatly eased when entrainment of some fraction of the substrate(s) through the fluid recycle loop is avoided, and an efficient cleaning is frequently operated.

## **10. Cleaning large-scale units**

One of the most important issues for operating a large-scale SCF flexible unit is probably cleaning and cleaning *validation* according to GMP, as most parts cannot be opened between each lot manufacture, and most high pressure parts - like valves - are not Clean-In-Place (CIP). According to our experience, we would propose the following cleaning procedures :

- Between batches of the same product :

Rinsing the unit with an adequate liquid solvent (chosen as a “good” solvent for the processed material), dismantling and cleaning dead-ends, rinsing again with the liquid solvent, with sampling for cleaning validation, drying with air, gaseous nitrogen or CO<sub>2</sub> to eliminate solvent vapor and rinsing with liquid/supercritical CO<sub>2</sub> that is finally vented to atmosphere in order to eliminate most extracted impurities (mainly liquid solvent) ;

- Between different products :

Dismantling the equipment, cleaning each part, swabbing the pressure vessels and all “critical” points, re-assembling the equipment, and application of the precedent cleaning procedure.

Cleaning is validated through liquid solvent samples analyses (dry weight and chemical identification of residue) and swab characterization according to the classical technique.

It is extremely important to consider the cleaning issue at the very beginning of any SCF equipment design : This influences many choices so as to avoid piping/instruments dead-

ends and all zones that could not be swept easily by the process and cleaning fluids. For example, we developed very low volume multi-tubing/multi-instrument connections, and very low volume high speed separators in form of cyclonic chambers. Moreover, adequate parts must be installed to permit an easy rinsing of the whole unit with liquid solvent : the ports locations must be carefully determined so that a total drainage is rapidly completed.

#### **IV. SCF EXTRACTION/FRACTIONATION SCALE-UP**

Supercritical Fluid Extraction processes can be scaled-up from lab-scale or pilot-scale results according to a simple procedure [27,29] : At first, small-scale experiments lead to the optimal extraction conditions through a scanning of different pressures, temperatures, solvent ratio and composition. Then, the scale-up method will depend on the mechanism controlling the extraction :

- Some extractions are only limited by the extract *solubility* in the fluid, as the solvent exiting the autoclave is saturated in extract. For instance, it is the case of lipids extraction when the access to the extract in the matrix is easy.
- Some extractions are only limited by *diffusion* and especially the internal diffusion. For example, stripping residual solvents from active particles or pesticide elimination from natural stuffs.
- Many extractions are limited by both *solubility* and *diffusion* : As shown on figure 2, the extraction versus time (or solvent to feed mass ratio) can be described as a first phase during which the extraction rate is constant (the solvent exiting the autoclave is saturated in extract at a concentration **a** equal to  $E_0/S_0$ ) and a second phase during which the extraction rate is decreasing due to diffusion limitation (the rate is the higher when the solvent flow rate is the lower). This is confirmed on figure 3 for spice extraction [28,29] : The extraction was performed on 7 typical ground spices



at various conditions of pressure and temperature chosen in the most common ranges (250 – 300 bar, 40 – 60 °C). The first part of the extraction curve is always a right line corresponding to CO<sub>2</sub> saturation at the autoclave exit, the slope **a** being the extract solubility in CO<sub>2</sub> in these extraction conditions. In this first part, the 7-spice extraction curves are almost superposed when the yield percentage (ratio of yield to final yield) is presented versus the product of the extract solubility **a** by the solvent ratio (CO<sub>2</sub> to feed mass ratio). Then the curves are not superposed as diffusion takes the control of the extraction. Depending on the complexity and on the kinetic limitations of the extraction, different methods are available to design the production unit :

- The easiest method to scale-up experimental data is to keep one or both of the ratios  $U_s/M_f$  and  $M_s/M_f$  constant, where  $U_s$  is the solvent flow rate (in kg.h<sup>-1</sup>),  $M_f$  the feed mass in the extractor (kg), and  $M_s$  the solvent mass required for the extraction (kg) :

➤ The ratio  $U_s/M_f$  is inversely proportional to the residence time of the solvent in the extractor  $t_r$  :

$$t_r = \varepsilon \cdot \rho_s \cdot M_f / (U_s \cdot \rho_f) \quad (1)$$

with :  $\varepsilon$  : Void fraction of the bed

$\rho_s$  : Specific gravity of the solvent

$\rho_f$  : Specific gravity of the feed

and shall be conserved for extraction limited by *internal diffusion* for which the "contact" time of the feed with the solvent is the determinant factor. Therefore, it will be necessary to use very large extractors or to use several extractors in series in order to maximize the contact time, meanwhile it is possible to minimize the solvent flow rate and the energy consumption of the plant.

- The ratio  $M_s/M_f$  is the ratio solvent/feed that has to be maintained in the case of extraction limited by the *solubility* of the extract. So, for a given plant capacity, and therefore a given amount of solvent and energy consumption, it will be often possible to reduce the volume and the number of extractors as much as possible. However, the autoclave(s) volume and dimensions (length H, section S) have to be designed so that the solvent spatial velocity (equal to  $H/t_r$ ) is low enough to limit the pressure drop and possible channeling through the feed bed.
- When both *diffusion* and *solubility* control the extraction, both ratios  $U_s/M_f$  and  $M_s/M_f$  shall be maintained constant.

This method has the definitive advantage of simplicity but does not take into account several important factors (internal diffusion, axial mixing, etc.), and is unable to predict the effect of using a series of autoclaves.

- A refined method integrating these factors requires a numerical simulation that can estimate any configuration and permit the industrial plant optimization. Different models have been proposed in the literature, and we built a versatile simulation software allowing to represent a lot of different systems [29].

Knowing the production requirements, the optimal configuration will be determined : the principal factors are :

- number of extractors,
- volume and number of shift/day of the extractors,
- pump and utilities capacities.

Traditional production units are composed of at least 2 extractors. One is unloaded/loaded while the other one is operated in extraction. Three or more extractor configurations are often preferred in order to reduce the dead-times and increase the extraction efficiency. These extractors are connected in series, so that the feed and the solvent are contacted

counter-currently : The last extractor of the series is loaded with “new” feed and the first extractor is loaded with feed that has already been contacted the longest time with the solvent and is the next to be unloaded. This "carrousel" implementation allows to reduce the amount of CO<sub>2</sub> required for a given extraction, and therefore, to increase productivity and reduce energy consumption. For a given production capacity, increasing the number of extractors will therefore decrease the energy consumption and the operating costs, but increase investment cost. The extractor volume also depends on the number of shift/day that can be operated. The economic estimation allows in each case to decide what is the optimal configuration.

As the extrapolation and optimization methods described above concern only the "extraction step" of the process, it is also very important to optimize the other parts of the process : Extract recovery and fractionation, energy management, improvement of the extractor emptying and loading procedures also have important economic consequences and must be considered in the industrial process design.

Regarding Supercritical fluid Fractionation that is performed on a counter-current column, scale-up is the more difficult as axial mixing in both phases dramatically decreases the fractionation efficiency – in terms of height equivalent to a theoretical plate -. At present time, no reliable results have been published yet on column scale-up. We would recommend the following procedure, following what has been done in liquid-liquid extraction for long :

- Determination of liquid and fluid hold-up curves at pilot-scale in order to estimate the flow rates at which flooding happens in the given pressure-temperature conditions with the chosen packing (random rings or non-random packing) ; we would stress on the fact that liquid foaming often happens, especially when the feed is a natural product or is prepared by fermentation as many biological compounds

act as surfactants ; similarly, impurities in form of solid particles or colloids may have the same effect ; as foaming may drastically modify the hydrodynamic pattern and lead to flooding, experimental runs must be performed with a “representative” liquid, not with a synthetic mixture of pure compounds ;

- Scale-up the column diameter on the basis of these curves, avoiding the zone where hold-up may happen ;
- Column length should be evaluated very prudently as axial mixing increases with column diameter. A great care must be taken to design the fluid and liquid phase distributors ; channeling shall be reduced by fractionating the packing in several beds separated by re-distribution plates ;
- Regarding reflux, large-diameter columns cannot be operated with the internal reflux caused by a temperature gradient along the column that is operative only for diameters below 15 cm. So, an external reflux through a pump re-injected part of the extract shall be implemented, what also permits an easy control of this parameter.

## **V. SCF DRUG FORMULATION SCALE-UP**

Particle formation processes using supercritical fluids are now subjected to an intense R&D effort in the pharmaceutical industry both for formulating water-insoluble (or poorly soluble) and hydrophilic molecules, including fragile bio-molecules. In fact, SCF drug formulation is a very wide domain leading to very different particles in terms of size, shape and morphology through several very different processes described in the precedent chapters and in many publications and reviews [17,18]. Presently, in spite of very attractive results obtained at lab-scale, commercial development is still pending as scale-up requires to solve some major issues that we will investigate in the following paragraphs. Almost no article was ever published on this domain, except a few ones dealing on anti-solvent

processes : The first two [30,31] claim success on scale-up from lab to pilot scale, but yet at a very small scale (a few grams per hour) and another one presents interesting considerations, listing scale-up issues but without tangible results [32]. A few brief economic studies [33-34] were also proposed, but based on contestable technical assumptions, especially regarding the fluid/substrate ratio, and no solutions to scale-up issues were presented ; the most recent one [34] is the more complete, although it significantly underestimates the equipment cost and does not evaluate the extra-cost related to compliance with GMP if a drug is processed. Although the SCF formulation processes are very different, all of them comprise three main steps for which scale-up is difficult : Particle generation, particle collection and fluid purification and recycle (when recycled).

#### **A) Micro-Particle generation**

For most SCF formulation processes leading to micro-particles (except batch anti-solvent GAS that is rarely used [35] and some coating [36-40] and impregnation processes [41-44]), particles are generated by *atomization* through a nozzle :

- Rapid Expansion of a Supercritical Solution (RESS) [45-47] ;
- Particle precipitation by Supercritical Anti-Solvent (SAS) according to various implementations like the batch Gas-Anti-Solvent (GAS) [48,49] and the continuous Aerosol Solvent Extraction System (ASES) [32,50-54] or Solvent Enhanced Dispersion by Supercritical fluids (SEDS) [30,31,55] ;
- Particles from water solution by anti-solvent [31,56,57] or nebulization [58-60] or extraction by a polar fluid [54,61], and from W/O emulsion droplets (emulsion drying process [13,62, 63]) ;
- Particles from a Gas-Saturated liquid Solution (PGSS) [64-66] or micro-capsules from a fluid-expanded suspension [67-69] ;

- Porous particles impregnated by a substrate by co-pulverization of the fluid-saturated substrate and the porous excipient, using the Concentrated Powder Form (CFP) process [70].

## **1. Atomization**

At lab-scale, the difficulty is to manufacture and operate very small-diameter nozzles (< 100  $\mu\text{m}$ ) that are often plugged by micro-particles ; for a given process and processing conditions, the nozzle diameter and shape (length-to-diameter ratio) and the fluid (or liquid) velocity through the nozzle determine the size and shape of the generated particles, but no model is presently available to correlate these process and nozzle parameters and particle properties for any of the processes. Although it looks very simple, RESS is very difficult to describe, as shown in recent detailed contributions [71,72], from which it is not possible to find easy scale-up rules. Similarly, anti-solvent modeling was subjected to extended investigations [73-76] that did not lead to practical results yet. In fact, the phenomena are extremely complex as the particles size and morphology result not only from the atomization itself – and the resulting particle nucleation – but also from their growth by condensation and/or coagulation during their residence time inside the atomization vessel.

Ideally, scale-up should be made in maintaining all parameters constant by replacing one nozzle by several similar nozzles of same design and dimension through which the fluid or liquid velocity, and pressure drop should be kept identical to those through the sole nozzle. However, it is difficult to realize practically an atomization system with several nozzles presenting exactly the same pressure drop and leading to a perfect fluid or liquid distribution, as it has been experienced in liquid-liquid or gas-liquid contactors ; moreover, in such multi-nozzle systems, the resulting droplets or bubbles do interact with each other

and may coalesce, leading to wide size distribution. In the case where multi-nozzle systems must be used, it is recommended to perform experiments with a unitary nozzle to optimize the process parameters in order to obtain the adequate particles, and to scale-up by multiplying the nozzle number working in these optimal conditions.

Another route, applicable to the RESS process, consists in using a sintered disk as fluid distributor as proposed by Domingo et al. [77], although this system performance is limited by the imperfect sintered disk porosity distribution that is continuously modified by the unavoidable plugging of the finest pores by nano-particles generated inside the disk.

Regarding nucleation of solid particles from liquid droplets (anti-solvent, nebulization, PGSS, micro-encapsulation processes), it is obvious that the droplets size is a basic parameter in the process. Some investigators reported results of experimental works supported by theoretical considerations on droplet formation by injection of a liquid into a pressurized fluid using a simple capillary nozzle [78] or a coaxial nozzle [79]. Both articles, following previous works on liquid droplets formation into an insoluble liquid or into a gas, suggest the correlation of the experimental results with two dimensionless numbers :

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

where  $\rho$  is the specific gravity of the fluid,  $U$  the relative velocity of the two fluids,  $\Phi$  the nozzle diameter,  $\mu$  the viscosity of the fluid and  $\sigma$  the interfacial tension between the two phases. The larger is the Weber number, the greater is the turbulence versus the capillary forces, and the smaller are the resulting droplets. Experimental results and modeling show that the diameter of the initial droplets and of the resulting particles increase when the Reynolds number is increased and decrease when the Weber number is decreased [79],

meanwhile the ratio  $(We)^{0.5}/Re$  is proposed to evaluate the zone where a free liquid jet is atomized into the fluid [78]. On the practical point-of-view, these results are not easy to use for scale-up, except by maintaining both  $Re$  and  $We$  constant : When all other parameters are constant, these leads to the obvious rule of maintaining both the nozzle diameter and the liquid velocity through the nozzle constant, leading to a multi-nozzle system as said before. However, our experience showed that the key-parameter seems to be the liquid velocity meanwhile the nozzle diameter can be scaled-up on a certain range without modifying the particle size significantly [80].

Regarding the post-nucleation growth of particles, it could be assumed that maintaining the residence time before particle collection would lead to the same final particles when all other parameters are kept constant, especially fluid/substrate ratio, temperature and pressure.

## **2. Temperature control**

As recently reviewed [81,82], several authors showed that the solid morphology (amorphous and crystalline pattern) is dependent on the temperature at which the particles are formed and maintained during their residence through the atomization vessel, what could explain the very scattered results found in literature as the temperature distribution changes from one experimental system to another. At the difference with lab-scale equipment where the vessel thermal inertia in comparison with the heat flux brought by the fluid permits to easily stabilize the temperature distribution, a careful design and operation are required at large-scale in order to obtain reproducible conditions in the atomization vessel that are required to reach reliable particle size and morphology.

In fact, this practically implies that the particle formation and the particle collection cannot be operated in the same vessel !



## **B) Particle collection**

When micronic or submicronic particles are produced, particle collection and harvesting is certainly the most acute issue ! Based on the considerable experience gathered in dust collection at any scale [83], different particle collection systems can be proposed depending on the final form wished by the operator : Dry powder, dry mixture of active substance and excipient particles, aqueous or solvent suspension.

Basically, four concepts are currently used to collect particles from a gas flow : Inertia (gravity settler, impact chambers and cyclones), electrostatic forces, liquid scrubbing and filtering through porous media. In the present case, we have great doubts about the feasibility of electrostatic precipitation for both technical (use of very high voltage, powder explosivity, re-agglomeration,...) and economic reasons. Gravity settling is only efficient for large particles ( $>100\ \mu\text{m}$ ) and requires very large chambers. Impact chambers and high-efficiency cyclones are adapted for medium-size particle (between 10 and  $100\ \mu\text{m}$ ), but the collection efficiency rapidly decreases below  $10\ \mu\text{m}$  and is nearly zero for  $1\ \mu\text{m}$ -diameter particles ; even wet-wall cyclones (leading to a liquid suspension) have a limited efficiency in this size range. Finally, for micronic and submicronic particles as those required for pulmonary delivery (for example figure 4 presents the size distribution of insulin particles obtained by emulsion drying [63]) the choice is limited to filtration for obtaining dry particles or to liquid scrubbing for obtaining a suspension.

### **1. Particle collection by filtration**

Bag filters are classically used for very fine particle collection. The filtering media are either woven textile or non-woven paper or fiber mats. In the present case, the filtering media should be chosen in materials both compatible with the processed fluids (especially for anti-solvent processes where the filter is contacted with SCF and organic solvents) and acceptable for drug manufacture. We currently tested various filter types : Woven or non-

woven polymer (like PTFE or Polyamides) fibers to form bags or paper bags (as for vacuum-cleaners), or woven stainless steel fibers to form a disk, or filter–paper supported by a sintered disk at the bottom of a basket at smaller-scale ; ceramic filters can also be considered favorably.

In spite of its great efficiency of particle collection, filtration has several main inconveniences that must be overcome for reaching a reliable production :

- It is a batch process and filtration conditions vary with time as the filter cake is building, with correlative pressure drop build-up and particle layer compression that often leads to particle agglomeration, especially if some residual solvent is present ;
- The particle residence time on the filter varies and may lead to possible morphology changes (crystal pattern) and non-homogeneous properties ; the worst case happens when the particles are collected before they are completely dried by the fluid (anti-solvent or drying processes), leading to particles agglomeration and “sintering” inside the filter-cake ;
- Particle harvesting is not easy, especially when very fine particles are collected. At small-scale, it is possible to close the bag after depressurizing the collection vessel and to transport it into a glove box where the powder can be recovered into an adequate vessel. At large-scale, this system appears not applicable in most cases and *in situ* harvesting is often mandatory.

These issues cannot be solved through a unique technique, but several routes are proposed and adapted case-by-case.

### ***1.1 Dual filtration vessels***

In order to transform a batch process into a semi-batch process, the particle-loaded fluid is directed to one of at least two collection vessels that are operated alternatively in fluid filtration and particle harvesting.

### ***1.2 Harvesting from filter***

Several methods can be used for particle harvesting, depending on the particle size and final form. For large-scale operation, it is possible to shake the loaded bag-filter and to entrain the released particles by a reverse flow of low-pressure neutral gas (carbon dioxide or nitrogen). However, this collection is often difficult again for very fine particles, possibly requiring a second collection/harvesting step.

### ***1.3 Deep-bed filtration***

In the case where the particles are to be mixed into an excipient prior to tableting, it could be interesting to replace the bag filtration by a deep-bed filtration through a bed of excipient, avoiding any further handling of these fine particles [84]. The bed depth depends on the excipient particles size distribution, but for “classical” fine powder, it can be set at a few tens of cm. Of course, the solid mixture can be easily removed and must be submitted to an intense mixing for obtaining an homogeneous repartition of the active substance inside the final powder. This very simple method is easily applicable to RESS process ; for anti-solvent particle formation, the organic solvent must be carefully stripped from the resulting solid mixture prior to the final powder recovery, as it may adsorb onto the excipient beads at a significant concentration.

### ***1.4 Carbonic snow collection***

As it is well-known that rain droplets or snow crystals formation is controlled by the presence of dust particles in the clouds that serve as nucleation germs, we demonstrated particle collection by capture into large particles of “carbonic snow” generated by depressurization of a stream of liquid CO<sub>2</sub> into the particle-loaded gas stream ; surprisingly, the collection efficiency was very high and the “snow” was easily collected in a cyclone [85]. After transfer of this snow in a clean vessel and slow sublimation, it results in a dry powder of micronic particles showing no agglomeration. This method looks of particular

interest when particles are formed by RESS, as collection can be made without any filter at the exit of the atomization vessel.

## **2. Particle collection by scrubbing**

Liquid scrubbing is also known as one of the most efficient method for very fine particle collection, but they are gathered in form of a suspension that can be rather used for nasal, pulmonary or parenteral delivery. The suspension stability is often a delicate issue as no chemical or biological degradation shall occur, nor particle decantation, what requires the use of complex mixtures including a buffer (especially for bio-molecules), preservatives (anti-microbial, anti-oxidant, etc.) and surfactants. Several systems have been described [37,86-88] :

- Direct injection of the particle-loaded gas resulting from RESS into an aqueous solution of a surfactant, especially lecithin [86] ;
- Co-injection through the same nozzle of the fluid solution containing the substance and a warm aqueous solution supplying the enthalpy required to completely vaporize the fluid without important pre-heating before the nozzle [87] ; this process is especially adapted when using a liquefied gas as solvent and/or a thermolabile substance is processed ; a surfactant or stabilizing agents can be added either in the fluid phase, or in the aqueous phase, or maybe in both ;
- Scrubbing the particle-loaded gas by a liquid solution in which is dissolved a coating agent that will entrap the particles either by co-acervation caused by anti-solvent precipitation [37] or by deposition caused by coating agent sursaturation caused by solvent extraction by the fluid [88].

## **C) Residual solvent stripping**

For processes using an organic solvent (*anti-solvent, emulsion drying,...*), one major issue is related to the elimination of residual solvent adsorbed onto the formed particles. At lab-scale, most investigators collect the particles at the bottom of the atomization vessel onto a filter and propose to percolate pure carbon dioxide after stopping the stream of organic solution ; in the rare publications dealing with data on 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, the worst case being when the substrate is precipitated from an aqueous solution and should be obtained with a low moisture content. 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 and formation of aggregates with unacceptable concentration of solvent, especially when submicronic or micronic particles are formed.

For these reasons and in order to decrease the ratio fluid/substrate (and the cost), we propose a two-step method for large-scale operation :

- At the end of the particle precipitation, a stream of pure CO<sub>2</sub> is pumped through the collection vessel in order to eliminate the fluid rich in organic solvent and a part of the solvent present onto the particles ; this requires only a low fluid/particle ratio ;
- Then after depressurization, the particles are harvested and the powder is set into a basket to be installed in an extraction autoclave and submitted to a flow of SCF CO<sub>2</sub> ; the ratio fluid/substrate can be reduced by changing several times the fluid direction upward/downward to prevent channeling, the fluid being recycled after solvent collection and purification as detailed in the next paragraph.

#### **D) Fluid purification and recycle**

For most SCF formulation processes at large-scale, solvent recycle is mandatory whatever are the encountered problems detailed below. Most investigators do ignore this major economic and technical issue as they only work at lab-scale where the fluid can be vented ; otherwise, many results would never have been presented as attractive and “promising” breakthroughs as they are certainly useless for any commercial application.

### **1. PGSS, CFP and micro-encapsulation processes :**

The fluid is carbon dioxide and the ratio fluid/substrate(s) is very small, of an order of magnitude of 1 : No need to recycle the fluid that is depressurized to atmosphere and vented [64-70].

### **2. RESS :**

In most cases, the fluid must be recycled : Either it is carbon dioxide and the substrate solubility is low so that a huge fluid/substrate ratio is required, currently of the order of magnitude of  $10^3$  to  $10^4$  or even higher, or it is another fluid with better solvent properties like propane or dimethyl ether leading to a lower ratio...but both demands fluid recycle ! In both cases, recycle is difficult and costly as the fluid must be recompressed from the atomization pressure to the dissolution pressure. In fact, this imposes that the atomization pressure is much higher than the atmospheric pressure, at the difference with what is currently done at the lab-scale (although the so-generated particles may be significantly different from those obtained when the solution is atomized at a much higher but “realistic” pressure). Another difficulty appears when the supercritical fluid is a mixture of two or more components (like carbon dioxide + propane or polar co-solvent) : On one hand, the collected particles have to be stripped from residual solvent(s) by pure carbon dioxide, and, on the other hand, the fluid mixture recycling demands a composition control.

### **3. Anti-solvent**

Carbon dioxide is generally used and the particle formation and collection is operated at high pressure permitting an “easy” recycle of the fluid...after purification. However, similarly to RESS, anti-solvent particle formation requires huge fluid/substrate ratios, especially when water solution are processed ; it is important to know that the fluid is not only required for the particle formation itself, but also for extraction of the solvent residue adsorbed onto the particles after collection. In fact, fluid recycle is difficult because it is quasi impossible to eliminate the organic solvent, borne by the fluid after particle collection, by the classical means used in Supercritical Fluid Extraction, as the residual solubility of the organic solvent in the depressurized fluid at the recycle pressure (~40 to 50 bar) is far from null. For the anti-solvent precipitation itself, the fluid can be recycled as it is, at the condition that the solvent concentration is perfectly constant ; we developed an original system to maintain the recycled fluid composition at a constant value, based on the Gibbs’ law, that was successfully demonstrated in preparative supercritical fluid chromatography [89]. For solvent stripping from the collected particles, pure carbon dioxide is required and can be recycled only after the classical solvent collection by fluid depressurization followed by carbon bed adsorption so as to drastically reduce the solvent content in the fluid and consequently inside the stripped particles. On large-scale units, this imposes two separate fluid circuits, one for anti-solvent precipitation, the second for stripping.

#### **4. Drying processes**

Several SCF processes are being developed for obtaining dry particles from aqueous solutions, but drastic limitations appear at scale-up.

##### ***4.1 Anti-solvent***

The fluid is a CO<sub>2</sub> – Ethanol mixture, the alcohol serving as entrainer of water into the fluid ; the same recycle system as proposed for the anti-solvent process is applicable. But, this

requires huge fluid/substrate ratios, of the order of magnitude of  $10^4$  to  $10^5$ , rendering scale-up economically hazardous.

#### ***4.2 Emulsion drying***

Supercritical CO<sub>2</sub> extracts the water and organic solvent (a heavy alcohol or ketone) and the same recycle system as proposed for the anti-solvent process is applicable. At the different with the precedent process, much lower fluid/substrate ratios, of the order of magnitude of  $10^2$  to  $10^3$  are required, with the resulting savings in the recycle loop.

#### ***4.3 Polar solvent drying***

As a polar fluid is a much better solvent of water than a CO<sub>2</sub> – Ethanol mixture, the fluid/substrate ratio is drastically reduced, of the order of magnitude of  $10^2$ , but the fluid-water separation is not easy. Similarly to what is proposed for anti-solvent, it is valuable to operate the particle formation with a recycled fluid, even with some moisture, but to eliminate the residual water from the particles in a second step with a pure dry fluid, possibly by using carbon dioxide that also strips the residual polar fluid adsorbed onto the particles at the same time, and eliminate explosion hazard during particle harvesting.

### **5. Impregnation and coating by deposition**

These processes [36, 39-44] do not raise any major difficulty for fluid recycle that can be operated with the same systems as currently used in Supercritical fluid Extraction.

#### **E) Scale-up results :**

For several years, we have been designing and operating equipment permitting to operate the various SCF particle design processes :

- Samples below one gram can be processed at very small-scale on new chemical entities or bio-molecules on an equipment (X0.1 figure 5) protected inside an



isolator (glove-box) with a sapphire cell and small atomization vessels (~10 ml) [90]

;

- Larger samples (one to twenty grams) are processed on a pilot plant (X1 figure 6) installed inside a “laminar” hood ;
- Clinical lots (ten to one hundred grams) can be prepared on a larger pilot plant (X10 figure 7) operated inside a clean room, in compliance with GMP ; for instance, we recently processed bovine and human insulin in order to obtain inhalable particles (particle size distribution presented on figure 4) from an aqueous solution using our emulsion drying process [13,62,63] ;
- Large lots can be prepared on a commercial-scale plant (X100 shown on figure 8) where several tens of kg of particles can be obtained daily, either by RESS, anti-solvent or micro-encapsulation ;
- For a non-pharmaceutical application, we are envisaging to modify a large SFE plant (X1000 on figure 9) for processing at least 1,000 kg of powder per day by an anti-solvent process ;
- Micro-encapsulation by atomization of a fluid-expanded suspension [66,67] is performed on the pilot plants (X1 and X10) with addition of large low-pressure vessels in which the mixture is depressurized and the particles collected. Larger lots were produced from a 60-liter agitated vessel as presented on figure 10. No major difficulty appears when scaling-up to this size that corresponds to the commercial scale for most bio-molecule encapsulation as several-kg lots can be processed daily.

In order to demonstrate that scale-up can be successfully performed from lab to commercial-scale, we performed the atomization of inulin - a poly-saccharide extracted from chicory root – from NMP solutions (300 g/l) by anti-solvent with supercritical carbon dioxide (20 MPa, 40°C): After first test at lab-scale (X0.1), we prepared samples on the

three plants : 2 g on X1, 20 g on X10 and 200 g on X100 [80]. As shown on figure 11, the particle size distributions (by volume) are strictly the same at the three scales in the range wished to obtain a “non-dusty” powder. Moreover, this work permits to show that the fluid/substance ratio (~50 kg/kg) can be optimized at a much lower value than generally stated in most publications (500 to 10,000).

Extended work is now on-going on therapeutic molecules and for smaller-size particles at large-scale.

### **Conclusion :**

Supercritical Fluid technology is not yet widespread in the pharmaceutical industry, except for extraction of active compounds from vegetal sources (phytopharma-/nutraceuticals). Many innovative drug formulations based on SCF technology are now under development, demanding a wide R&D effort as process choice and optimization shall be adapted case-by-case on technical and economic basis as summarized on table 2. Ironically, this intense R&D work is leading to many attractive results, but also to many patents that are rendering the Intellectual Property situation rather complex, and may refrain pharmaceutical companies to enter this technology in their formulation “tool-box” on the short term. But, more importantly, the process complexity conjugated with the high investment required have probably delayed the introduction of the SCF formulation techniques in spite of their proven performances and interests for designing innovative drugs.

But the situation is moving and the “pipe-line” is now rich of several formulations to be shortly introduced for registration, especially for manufacturing inhalable and sustained-release particles. We already built three semi-industrial particle-design plants under strict quality assurance and documentation that are presently used for clinical lots manufacture, and scale-up with compliance to GMP seem accessible at present, as shown through this

article and the next chapter of this book. Moreover, as most promising drugs are based on proteins and peptides delivered by injection, the intrinsic sterility of SCF processes will appear as a major advantage for preferring these environment-friendly solutions.

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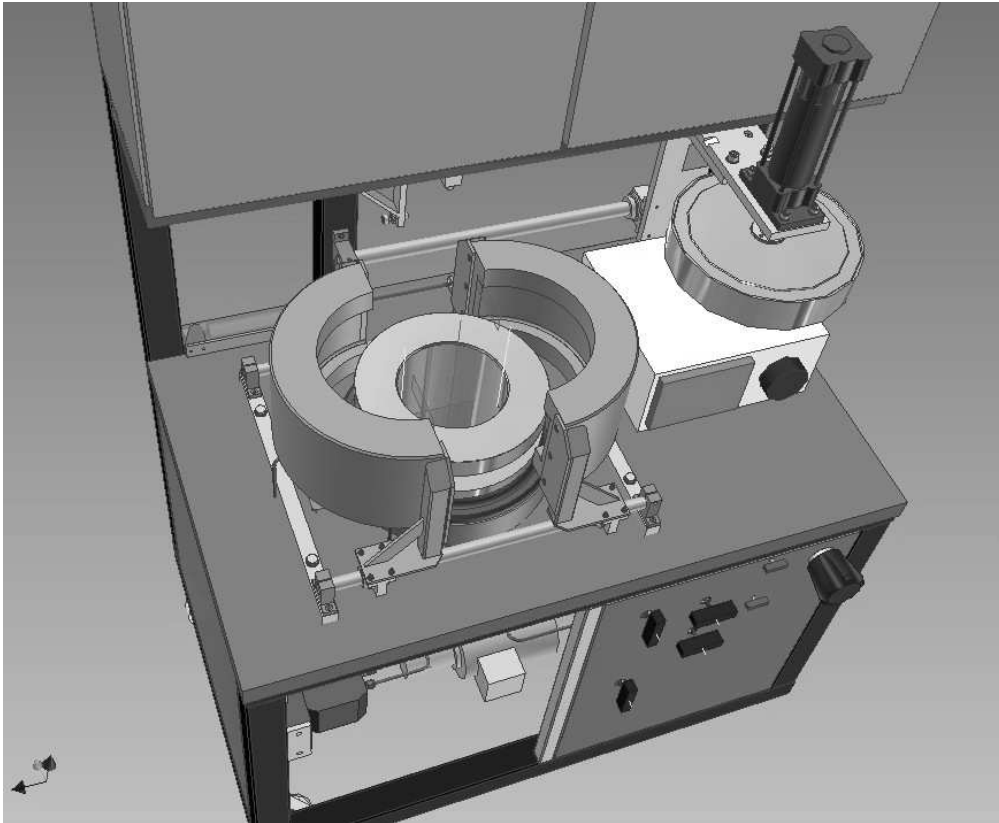
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*Table 1: Critical conditions of usual SCF solvents*

<b>Compound</b>	<b>Mw</b>	<b>Pc (MPa)</b>	<b>Tc (K)</b>	<b><math>\rho_c</math> (kg.m<sup>-3</sup>)</b>
<i>Carbon dioxide</i>	44.01	7.38	304.1	468.7
<i>Propane</i>	44.09	4.25	369.8	217.2
<i>Dimethyl ether</i>	46.07	5.24	400.0	255.8
<i>Difluoromethane</i>	52.02	5.83	351.6	430.7
<i>Trifluoromethane</i>	70.01	4.86	299.3	527.6
<i>CF<sub>3</sub> - CH<sub>2</sub>F (F134a)</i>	102.00	4.06	374.2	515.0
<i>Water</i>	18.015	22.12	647.3	315.5

**Table 2 : Formation of neat or composite micro-particles**

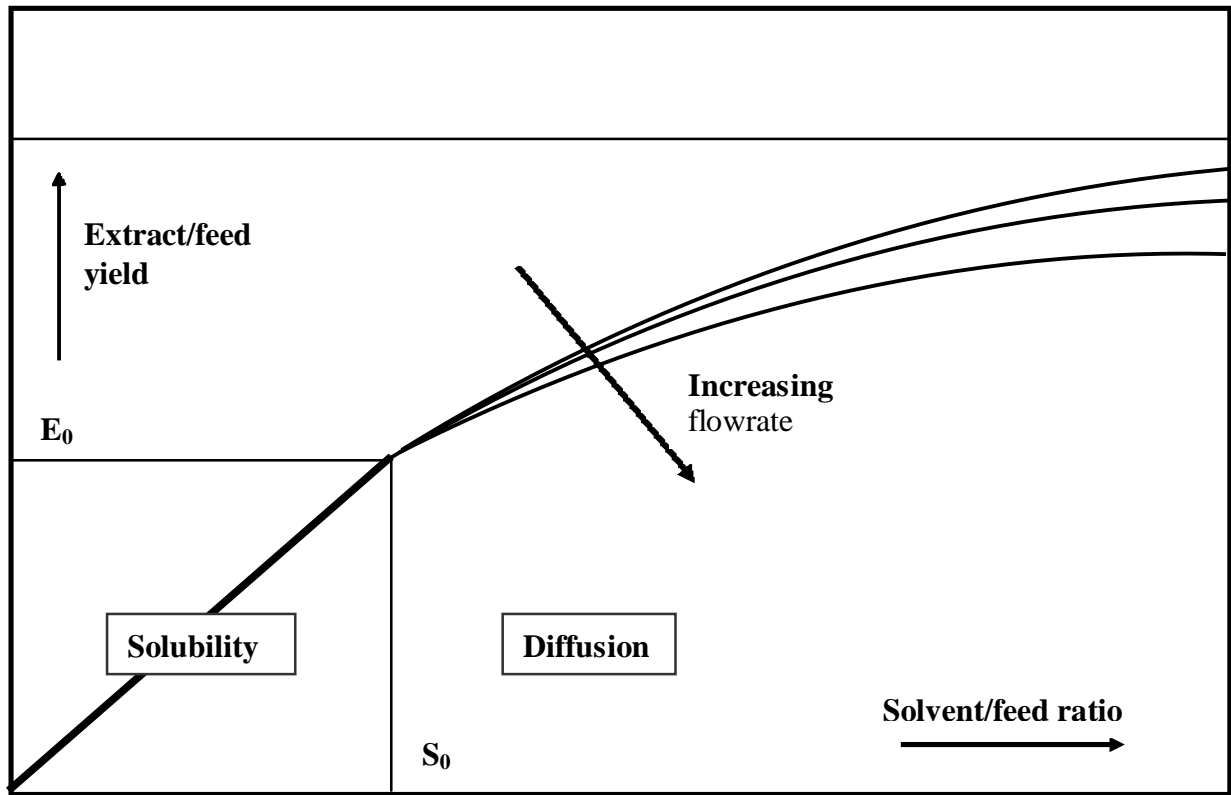
<b>Substrate soluble in SCF</b>	<b>Matrix soluble in SCF</b>	<b>Available process</b>	<b>Type of particles produced</b>	<b>Remarks</b>
<b>Yes</b>	<b>--</b>	RESS	Nano/Micro-particles	Few substrates/coatings are soluble in SCF CO <sub>2</sub>
<b>Yes</b>	<b>Yes</b>		Micro-spheres	
<b>Yes</b>	<b>No</b>	Impregnation	Micro-spheres	Difficult scale-up
<b>No</b>	<b>Yes</b>	Liposome-RESS	Liposomes	No scale-up development ?
		RESS Fluidized-bed coating	Micro-capsules	Few coatings are soluble in SCF CO <sub>2</sub>
		Coating deposition	Micro-capsules	Huge fluid ratio
<b>No</b>	<b>No</b>	Anti-solvent processes	Nano/Micro-particles Micro-spheres	Huge fluid ratio Difficult scale-up
		Coating coacervation	Micro-capsules	To be demonstrated at large scale
		Fluid-Assisted Micro-encapsulation	Micro-capsules	Very low CO <sub>2</sub> consumption Easy scale-up
		CPF process	Micro-spheres	Easy scale-up
<b>No</b>	<b>--</b>	Emulsion drying	Nano/Micro-particles	Biological molecules
<b>No</b>	<b>--</b>	Polar SCF drying	Nano-Micro-particles	Biological molecules
<b>No</b>	<b>Yes</b>		Micro-capsules	Difficult fluid recycle



*Figure 1 : Autoclave with clamp-closure system*

*(Courtesy of SEPAREX)*

Figure 2 : Typical extraction curves





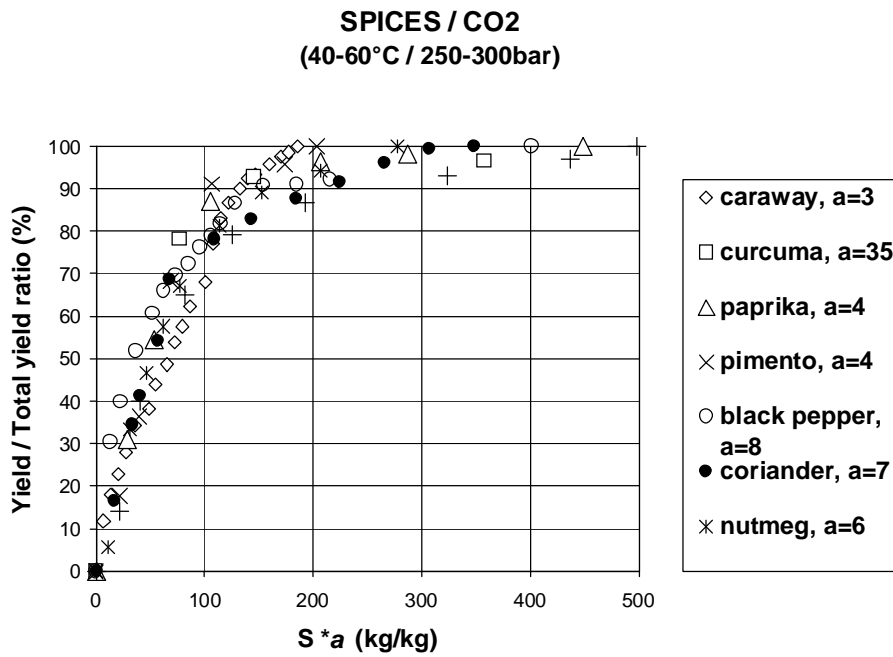


Figure 3. Spices extraction by supercritical CO<sub>2</sub> [28 ]

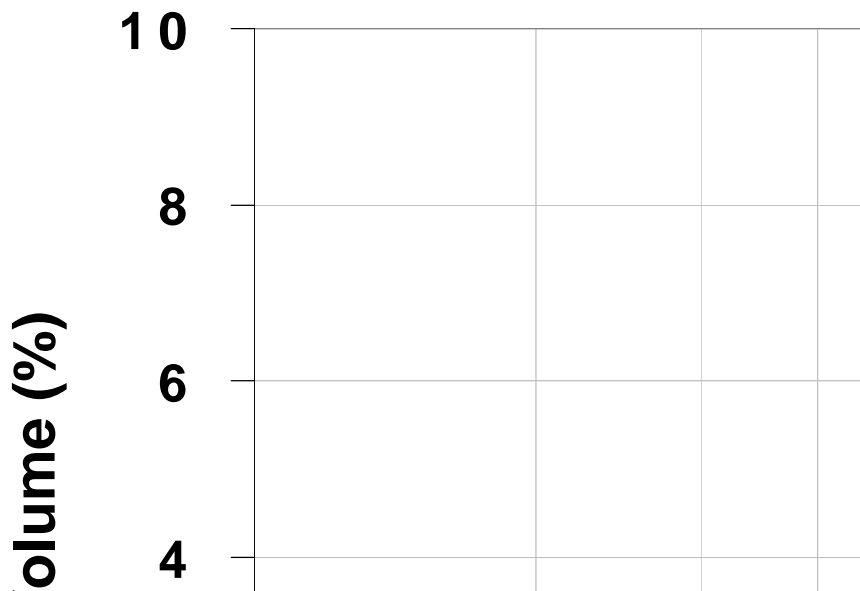
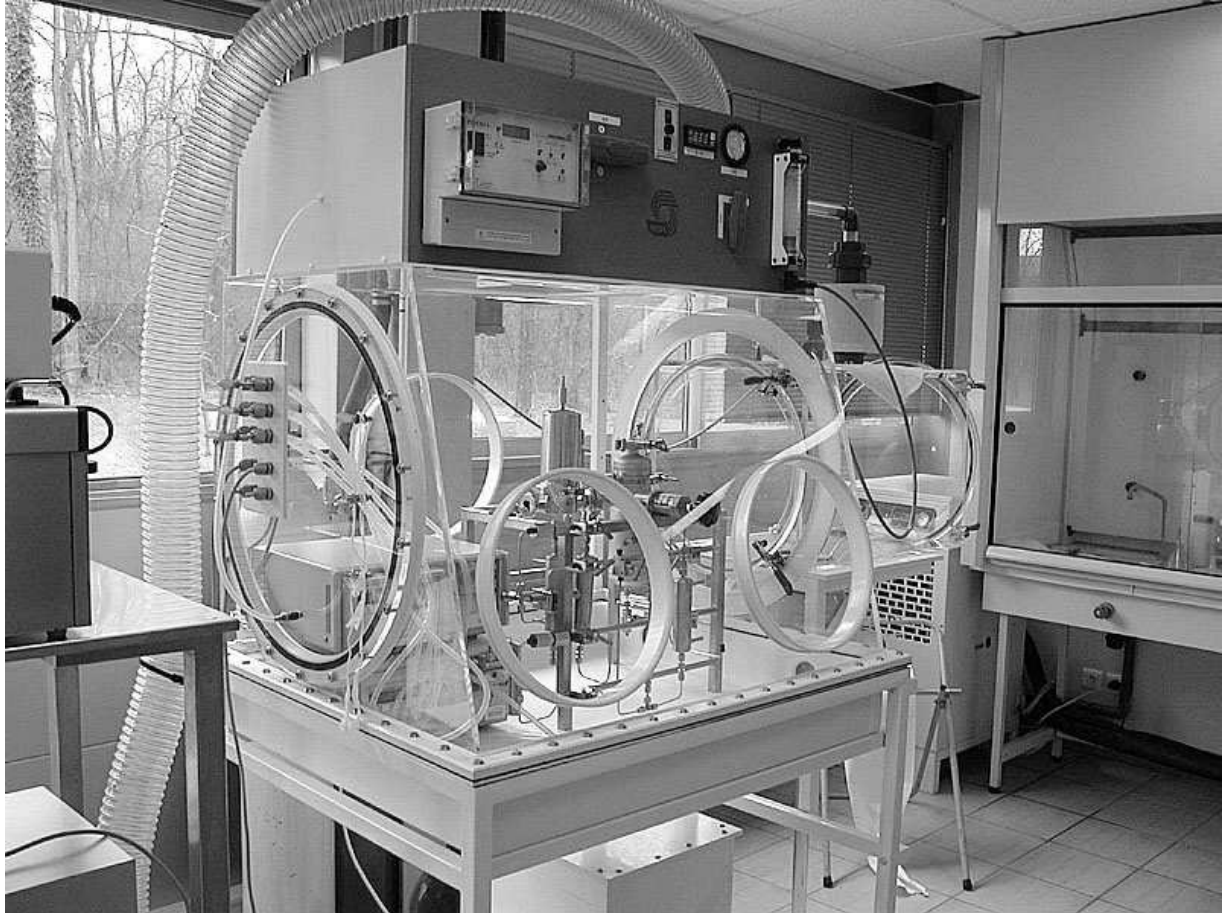


Figure 4 : Size distribution Insulin particles obtained by emulsion drying [63]



*Figure 5 : Lab-scale equipment (X0.1) inside an isolator [90]*

*Fluid flow rate : 0.5 kg/h - Atomization vessel : 0.01 - 0.10 liter*

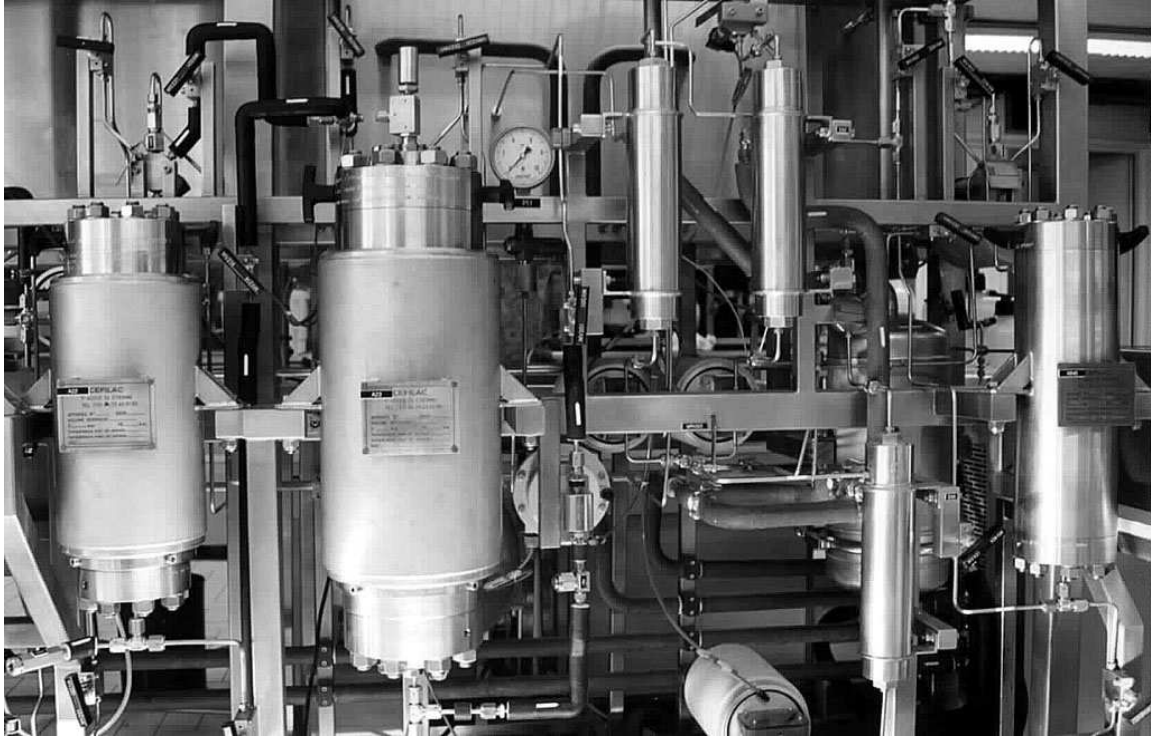
*(Courtesy of SEPAREX)*



*Figure 6 : Pilot-scale equipment (X1)*

*CO<sub>2</sub> flow rate : 5 kg/h - Atomization vessel : 0.5 liter*

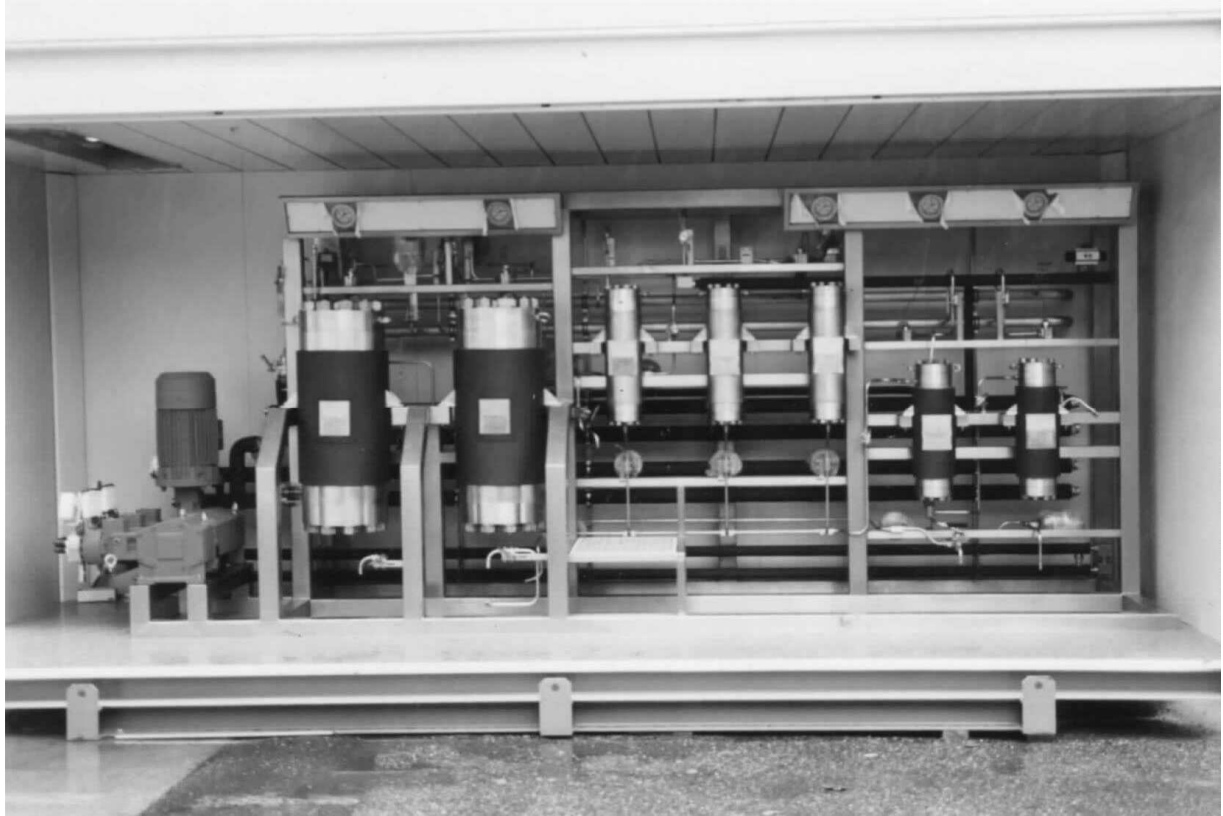
*(Courtesy of SEPAREX)*



*Figure 7 : GMP pilot plant (X10)*

*CO<sub>2</sub> flow rate : 50 kg/h - Atomization vessel : 5 liter*

*(Courtesy of SEPAREX)*



*Figure 8 : SCF plant (X100)*

*CO<sub>2</sub> flow rate : 500 kg/h - Atomization vessel : 50 liter*

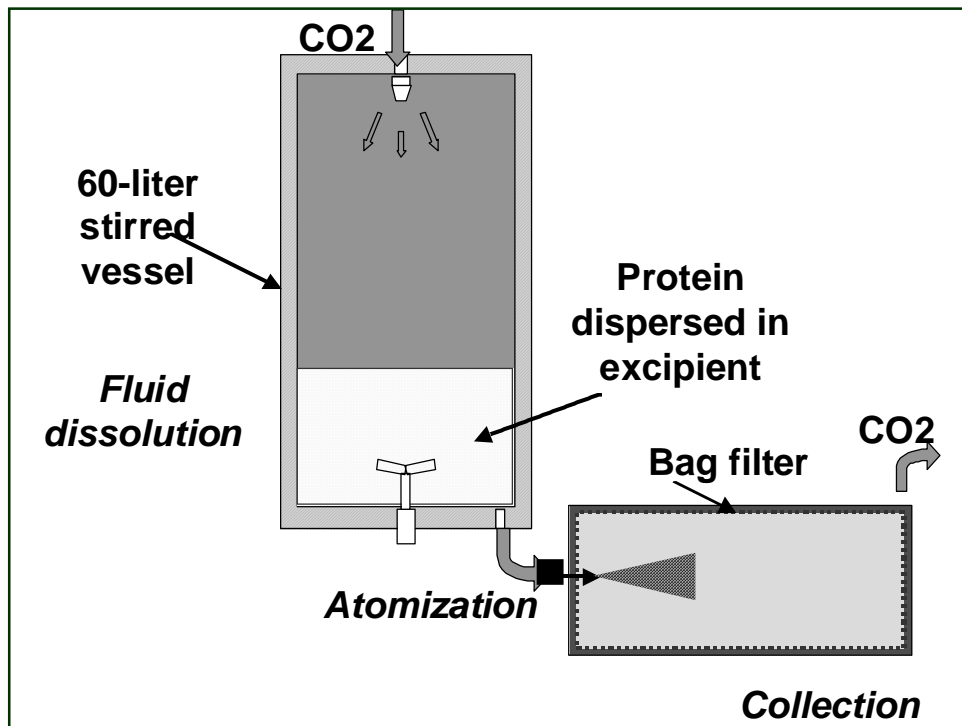
*(Courtesy of SEPAREX)*



*Figure 9 : SCF plant (X1000)*

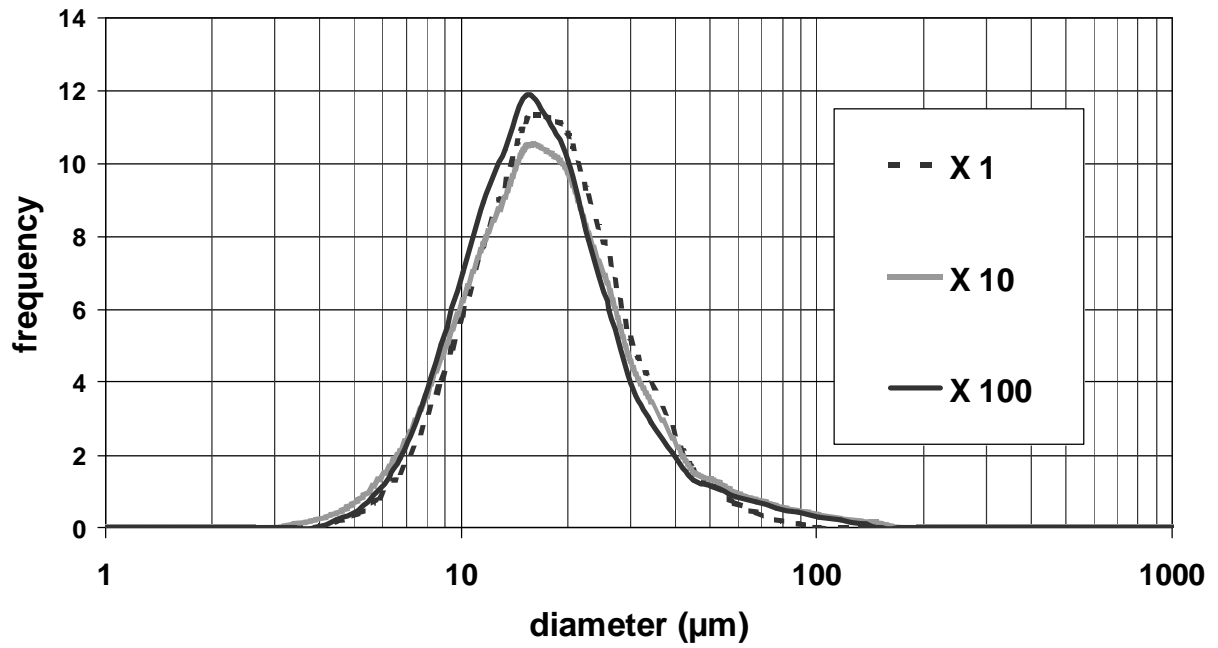
*CO<sub>2</sub> flow rate : 3,000 kg/h - Atomization vessel : 500 liter*

*(Courtesy HITEX & NOVELECT – Photo M. Philippe Baudet)*



*Figure 10 : Micro-encapsulation by atomization of a fluid-expanded suspension [67,68]*

*Dissolution agitated vessel : 60 l – Atomization vessel : 100 l*



*Figure 11 : Particle size distribution of Inulin particles prepared by ASES process on various scale plants : X 1 (2 g sample), X 10 (20 g sample), X 100 (200 g sample) [80].*