SUPERCRITICAL FLUID APPLICATIONS : INDUSTRIAL DEVELOPMENT AND ECONOMIC ISSUES.

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Abstract :

This lecture intends to give a brief overview of the status of Supercritical Fluid industrial applications and to draw some prospective trends. Based on the know-how gathered by SEPAREX along these 20 last years of work on many supercritical fluids applications and manufacture of more than 80 plants at pilot scale or industrial scale, economic evaluations and comments about design, maintenance and operation of supercritical fluid plants will be presented.

Present status of industrial applications :

During the last two decades, except for processes used in the petroleum industry - that are not in the scope of this lecture - industrial applications have been mostly developed for **natural products extraction/fractionation**, both for food and pharmaceutical products (Hundreds of references are available in literature ; I advice the reader to begin by [1-7]) . At present time, these applications are still continuing to slowly spread worldwide with a wide potential of capacity increase as high quality products are more and more required and environment/health problems are more and more taken into account.

• **Extraction** (SFE) from solid materials is the most developed application, mainly for food products (coffee, tea,…), food ingredients (hops and aromas, colorants, vitamin-rich extracts, specific lipids, …) and nutraceuticals/ phytopharmaceuticals. Residual organic solvent or other impurities, like pesticides, are also removed from final active compounds or food ingredients/nutraceuticals (like ginseng) at large scale [1-7]. I estimate the number of industrial-scale SFE units now under operation on natural products about 100 (or slightly over) with a growth of about 10% per year.

Some “niches” applications concern high-added value products, like delipidation of bones for allografts preparation, or specialty polymer stripping.

- **Fractionation** (SFF) of liquid mixtures are designed to take profit of the very high selectivity of supercritical fluids with attractive costs related to continuous operation ; nevertheless, few industrial units are now used for aromas production from fermented and distilled beverages, fractionation of polyunsaturated fatty acids and polar lipids, polymer fractionation (specialty lubricants, pharmaceuticals,…), recovery of active compounds from fermentation broths, pollution abatement on aqueous streams,….

- **Preparative Scale Supercritical Fluid Chromatography** (PSFC) is operated for ultimate fractionation of very similar compounds, especially for lipids like polyunsaturated fatty acids in a few large-scale units.

- **Reactions** (SFR) are operated in Supercritical media [4-6], mainly in large-scale petrochemical plants (butene hydration to 2-butanol, polymerization of PE, PVDF and other fluoro-polymers...), and in fine chemistry (highly selective synthesis [8]).

- **Paints and coatings :** Various large-scale applications are related to paint preparation and application :
  - Powder coatings : A US Company recently disclosed a large facility : 2 agitated -14m^3 autoclaves for preparing the CO_2 suspension of polymer and pigment mixture, one 50m^3 autoclave as atomization vessel [9].
  - Painting process developed by Union Carbide (UNICARB® process) [10] and Nordson [11] : Dissolving CO_2 under high pressure reduces the paint viscosity and permits a good application through pulverization of this solution at atmospheric pressure, permitting a drastic reduction (30 to 60 %) of organic solvent concentration in the paints and of VOC emission.

New applications :

Apart from the already-cited applications, many "new" applications of supercritical fluids are now either under commercial development in many areas, sometimes really unexpected.

- **Polymer processing :**

  Specific interactions between supercritical fluids and polymers lead to many attractive development [12]. Most polymers are swollen by SCF that act as **plasticizers**, decreasing sharply the glass transition temperature, what permits easy penetration of solutes (impregnation) or extraction of residues (stripping), morphology modifications (foams, particles, fibers, ...), blending alloys, grafting reactions or spinning fibers.

- **Ceramics and carbons manufacture :**

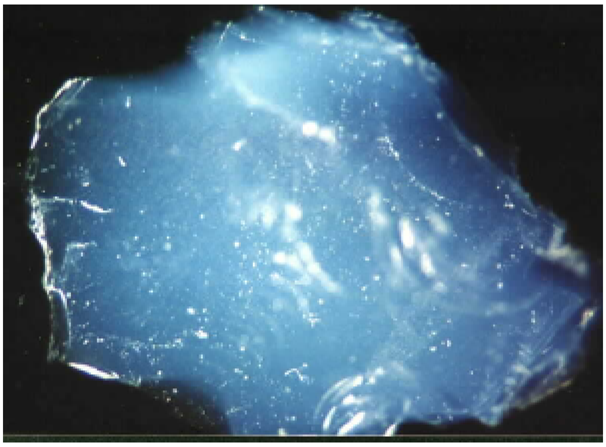
  For long, ceramic binder extraction has been widely described, permitting to manufacture ceramic pieces of very good dimension stability and reproducibility with a much shorter cycle than classical binder cracking by heating [13]. According to our knowledge, this process is getting increasing acceptance for high-duty ceramic parts.

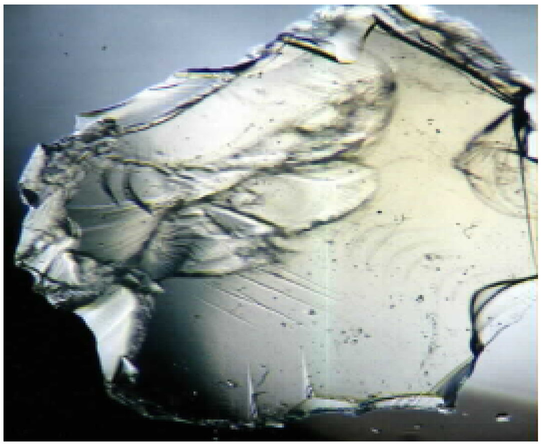
  On the other hand, ceramic precursors can be prepared using SCF, either through elaboration of the oxides powder by hydrothermal synthesis in supercritical water [14-18] or SCF CO_2 fractionation of narrow cuts of polymeric precursors of C-C alloys like polycarbosilanes or mesophase from petroleum pitch [19]. Moreover, impregnation of three dimension mats of carbon fibers by polycarbosilane is claimed to lead to a drastic improved C-C alloy properties (fatigue and oxidation under high stress) [20].

- **Foams and aerogels :**

  For long, all polymeric **foams** were blown with CFC (R12, then R22) that are now banned and most manufacturers are now turning to light hydrocarbons or, preferably, to carbon dioxide, leading to drastic cost reduction. Injection of CO_2 in thermoplastic extruders is now common practice, especially for polystyrene foam. On the other hand, more sophisticated polymeric foam elaboration using SCF was patented: preparation of micro-cellular foams (2-25 μm) from most thermoplastics was claimed as soon as 1984 [21] and, more recently, preparation of extremely small cells (< 2 μm) and extreme high cell density [22]. Moreover, it is possible to impregnate the foam with solutes during the foaming process if the solutes are soluble in liquid or supercritical CO_2 , as proposed for food products [23].

For long, supercritical drying of sol-gel into **aerogel** have been investigated for silica aerogels [24,25] and organic polymers [26-28] for various purposes, mainly for making high-performance heat insulation materials (double glass panes, refrigerators) ; in a less common application, *in situ* supercritical drying of a silica aerogel, recently operated by SEPAREX for oil/gas production well insulation. It is probable that large-scale production for insulation materials be developed in the next decade even if monolith drying is far from perfectly mastered [29].





SILICA AEROGEL SAMPLES

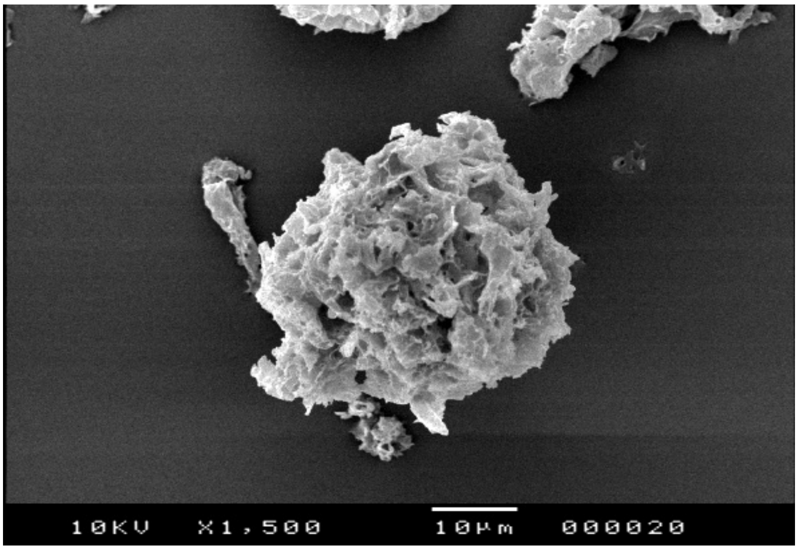
- **Particle design :**

Among the most original applications of supercritical fluids, particle formation processes using supercritical fluids [30] are now subjected to an increasing interest especially in the pharmaceutical industry with both aims : Increasing bio-availability of poorly-soluble molecules and designing sustained-release formulations.

- **Rapid Expansion of Supercritical Solutions (RESS)** was developed in the eighties, mainly for pharmaceuticals. It consists in atomizing a solution of the product in a supercritical fluid into a low-pressure vessel. RESS process could find valuable applications at commercial scale only when product solubility in supercritical CO_2 is not too small ($\geq 10^{-3}$ kg/kg) at "acceptable" pressures, limiting the process application to non-polar or low polarity compounds. Moreover, co-precipitation of a drug and a biocompatible polymer (poly-D, L lactic acid) was reported to lead to polymer-drug micro-particles ranging in size from 10 to 100 μm [31,32], opening attractive route for new drug delivery systems.

- **Supercritical Anti-Solvent (SAS)** process was firstly investigated for explosive comminuting [33]. In fact, at the difference with RESS process, the SAS process applies to most molecules, that can be dissolved in a very wide range of "strong" organic solvents. Recent developments, especially for drug delivery system preparation open a bright future for "engineering" new types of materials.
  Moreover, a great variety of morphology (crystalline, amorphous) can be obtained depending on operating parameters, nozzle shape and material properties, leading to attractive "engineered" structures [34,35], including :
  - nano-spheres (50-200 nm) or micro-spheres (500-5000 nm),
  - empty “balloons” (5-50 μm) made of nano-particles,
  - micro-fibers and hollow micro-fibers with diameters of 0.01 μm or larger [36, 37].

- **Particle Generation from Supercritical Solutions or Suspensions (PGSS)** consists in atomizing a solution of compressed gas or supercritical fluid inside the product to be treated, either in form of a liquid or a solid slurry, by decompression towards a low-pressure vessel, the rapid fluid demixion generating very small particles [38].
- Finally, we will just cite a very promising area for particle design using SCF : **micro-encapsulation** especially for drug delivery systems, using RESS, SAS, PGSS, some variants like for example the liposome generation [39] or carrier deposition by variation of pressure/temperature conditions [40].



PROTEIN ENCAPSULATED IN A LIPID EXCIPIENT

- **Impregnation :**

  High diffusivity and tunable solvent power of SCF are the basis of supercritical impregnation : In supercritical state, the fluid is a powerful solvent of the product to impregnate and an excellent vector, even in the smallest pores of the matrix (when porous) ; moreover, for polymeric non-porous matrixes, the swelling effect permits an easy penetration of the solute throughout the solid. On the other hand, as soon as decompression, the solute precipitates and does not follow the fluid exiting from the matrix. Many impregnation applications have been reported including polymer-wood composite preparation by monomer impregnation followed by in-situ polymerization [36], pharmaceutical patches, sponges, and catheters [42,43] or carbon-carbon or ceramic precursors [20,44]. We recently obtained attractive results on paper impregnation for development of a deacidification and reinforcement process for damaged books [45], and patented a new process for on-line impregnation after extraction, especially attractive for natural products processing as one sole operation leads directly to the usable product (active on excipient powder) [46].

- **Dyeing :**

  In order to reduce water pollution hazards and dyeing difficulty for certain synthetic fibers, a new family of colorants was developed and patented by CIBA [47] soluble in supercritical CO_2 and exhibiting an excellent affinity with these synthetic fibers. The dyeing process [48,49] has been widely investigated, but some major difficulties remain to be solved before a wide development.

- **Cleaning :**

  As halogenated solvents are widely banned either for health or environmental hazards, both textile dry cleaning and mechanical and electronic parts degreasing and cleaning, are becoming a worldwide issue. In spite of drastic efforts to find non-hazardous solvents (hydrocarbons, perfluorinated hydrocarbons or ethers, ...) or to re-investigate cleaning processes using water + surfactants, carbon dioxide is becoming one of the most attractive substitute to chlorinated and CFC solvents. Many patents and articles are now appearing, mainly in USA where a very significant effort is made to substitute perchlorethylene for dry cleaning and trichlorethylene for part degreasing, by liquid CO_2. However, the industrial development of processes using CO_2 has been slower than expected as just now are proposed real easy-to-operate cleaning machines at an acceptable price and a range of surfactants adapted to the various problems met by users.

- **Pollution abatement :**

In fact, the impact of supercritical fluids and especially of **carbon dioxide** on environment protection is positive both for pollution abatement processes and for environment-friendly processes : Organic solvent substitution in painting industry, polymer foaming, cleaning and degreasing, dry cleaning, recycling processes and substitution to water or air polluting processes (textile dyeing or fiber spinning for example) [50].

Soil decontamination by CO_2 extraction is attractive as soil can be disposed easily after treatment and transportable units were proposed for limiting soil transportation costs. However, it is to be stressed on the fact that only organic pollutants of low polarity can be easily removed and, even if some progresses were disclosed on chelatant use, it is not probable that heavy metals be subjected to supercritical fluid extraction in reasonable technical and economical conditions.

Similarly, treatment of viscous slurries of industrial wastes in order to extract the organic contaminants receives a great attention : We developed several processes using a versatile multi-solvent pilot plant equipped with a magnetic driven stirred autoclave : recovery of lubricant oil from oil drilling cuttings, of dielectric oil from electro-erosion machine wastes and cutting oil from metallurgical wastes [53].

Water streams polluted with organic compounds can be treated with CO_2 in order to recover the pollutants prior to water disposal. In most cases, the pollutant concentration is very small and total incineration of the stream is extremely expensive, pushing extraction for concentrating 100 to 10 000 times the final stream further sent to incineration. An industrial unit (5 m^3/h) is operated in Baltimore for toxic products removal from water with liquid CO_2.

Regarding air pollution abatement, supercritical fluids may be used for adsorbent regeneration. However, drastic engineering problems remain to be solved, especially the design of adsorption autoclaves and closure systems that must both lead to a very low pressure drop when adsorption is performed and to stand high pressure during desorption.

On the other hand, supercritical (or subcritical) **water** appears as a unique medium for safe destruction of dangerous wastes by total oxidation. Due to its special physicochemical properties, **supercritical water** has been proposed for long as a medium for total oxidation (SCWO) [18,19] ; however, experience showed that process development is extremely difficult due to corrosion (when sulphur, chlorine, phosphorous are present in the waste) and to plugging (salt deposition). In the more difficult cases, even the use of very resistant alloys is not sufficient to prevent corrosion and the reaction must be conducted inside a ceramic reactor, itself supported by a metal autoclave ; these problems result in high processing costs, in comparison with classical incineration ; however, industrial development is on the way for highly hazardous wastes, like toxic warfare gases or nuclear organic wastes.

On the other hand, it is to be noticed that pollutant destruction in **subcritical water** is receiving a keen interest : even if the oxidation rate is lower, temperature and pressure are significantly lower than in SCWO processes. This should be considered in parallel with the interest of subcritical water as an attractive reaction medium.

- **Reaction media :**

It is well known for long that supercritical fluids provide a new type of solvents for conducting reactions. Hundreds of articles have been published [4-6], reporting all types of reactions, with a special interest on enzymatic reactions in carbon dioxide, oxidation in supercritical water and polymerization in supercritical monomers or CO_2.

I would stress on the main reason that drives SCF use as reaction media : supercritical fluids are **tunable** solvents. Following a recent lecture by ECKERT [51], SCF properties give many opportunities to tuning reactions :

- Density and/or co-solvent tuning of reactions for rate, yield, selectivity ;
- Benign replacement of environmentally undesirable solvents ;
- Improved mass transfer for heterogeneous reactions ;
- Transforming heterogeneous reactions into homogenous reactions ;
- Simultaneous separation with reaction.

The use of new CO_2-philic surfactants opens the route to emulsion or suspension polymerization in supercritical or liquid CO_2 leading to "new" polymers [52]. Another domain of great potential is hydrogenation either for highly selective (asymmetric) synthesis [8] or large-scale hydrogenation of fats with a drastic increase of reaction rate [54].

So, there is no doubt that the use of SCF as reaction media will lead to major industrial developments during the next decades.

- **Biological applications :**

  As biotechnological synthesis of numerous therapeutic products are in progress, **cell lysis** by supercritical fluids (carbon dioxide, in fact) are the more interesting that this process does not heat the medium and does not lead to very small membrane fragments at the difference with classical homogenization : Preservation of fragile molecules and easier downward processing are attractive [55, 56] ; moreover, this can be combined with protein delipidation as CO_2 is a selective non-polar solvent.

  Regarding **sterilization**, it is known for long [57-60] that CO_2 could drastically help high pressure decontamination [60], as, for example, the bacteria (E. Coli) decay obtained after 15 min of processing at a pressure of 15 MPa with CO_2 is similar to that obtained at a pressure of 300 MPa during the same time [61].

  Meanwhile viral diseases are spreading fear worldwide, especially regarding contamination via blood transfusion and biomaterials, it was proven that **virus inactivation** can be performed by contacting with supercritical fluids :

  - Plasma fractions [62-64], including plasma delipidation [63, 64] with N_2O or CO_2 in “mild” conditions to avoid denaturation of the very fragile clotting factors and other proteins ; even if a high degree of inactivation has been proven for many viruses, much optimization work remains to be done before this method could be considered as available for clinical products processing ;
  - Bone implants, using CO_2 as delipidation solvent, followed by hydrogen peroxide, sodium hydroxide and ethanol treatment, what leads to an almost complete virus elimination ; the CO_2 step itself has a high virus reduction effect (more than 4 $\log_{10}$) on various strains including HIV-1 and Polio Sabin [65]. These results secure the use of such implants on humans.

  In order to apply Supercritical Fluid Extraction processes at large scale. I will also stress on the fact that an industrial unit must be designed with taking into account operation, maintenance and cleaning.

Economic evaluations :

Most companies believe that Supercritical fluid technology is very expensive due to very high investment costs in comparison with classical low-pressure equipment, and , even it leads to high-quality products, should be restricted to high-added value products. Yet, this is far from true when very large volumes of materials are treated, as in the case of coffee/tea and hops processing, paint manufacture, soil remediation and waste treatment !

High investment costs growing slowly with capacity increase….

Reliable cost estimation of supercritical fluid equipment is not presently available from published sources, and figures can drastically change according to the type of equipment, instrumentation automation,…. Here we will present the data we have gathered from our own experience of building pilot and industrial-scale SFE/SFF, on-line SFE/impregnation (SFI) and particle atomization (PA) units.

The following data are related to SF equipment consisting in :

- Extractors and/or column, reactors, atomizing chambers,… of total net volume V_T (liter);
- Separation steps with automatic extract withdrawal system ;
- One liquid CO_2 reservoir ;
- One CO_2 pump delivering a variable flowrate from 30 % to 100 % of the design flowrate Q ($kg.h^{-1}$), at the service pressure ;
- Several heat exchangers : condenser, sub-cooler and heaters ;
- All related piping, valves, instruments, utility services required for a reliable and safe operation in automatic mode, in order to minimize manpower and maintenance costs.

The observed costs of such units, delivered on a turnkey basis, are reported on figure 1 where, surprisingly, all prices (here represented by a dimensionless price index PI on a logarithmitic scale) are near to a straight line with a slope of 0.24 versus the log of product of total volume $\boldsymbol{V_T}$ by the design flowrate $\boldsymbol{Q}$:

$$PI = A.(10.\ V_T .Q)^{0.24}$$

As for similar units, the solvent flowrate $\boldsymbol{Q}$ is proportional to the total extractors (+ column) volume $\boldsymbol{V_T}$, this demonstrates that the cost of a SF unit roughly increases as the square root of the capacity. In fact, this confirms a feeling that has been shared for long ; however, it is surprising that this rule applies on such a large range of capacities, from the bench scale (0.5-liter autoclave) to industrial scale (500-liter autoclaves), but it underestimate prices of the small bench-scale equipment (0.2-liter autoclave). Nevertheless, I would guess that the price of much larger units, like those for hops or coffee/tea processing are probably much less costly than predicted by this rule. On the other hand, a significant price increase appears when special requirements are needed, as, for example, for combination of extraction and extract impregnation (SFI), or for unit built according to GMP requirements, as shown on figure 1.

This shows that capital amortization sharply decreases when capacity increases, what is a strong incentive to use large capacity multi-products units in “time-sharing” rather than operating small capacity units dedicated to only one product, when possible !

Obviously, this is clearly not possible when drastic requirements are imposed, especially for processing pharmaceuticals in compliance with GMP rules ; moreover, such units must be built according to a drastic quality assurance plan and are generally priced much more than food-grade units, from 30 to 100 %, depending on the size, as shown on figure 1 for two particle atomization (PA) units : one built without and one with these requirements.

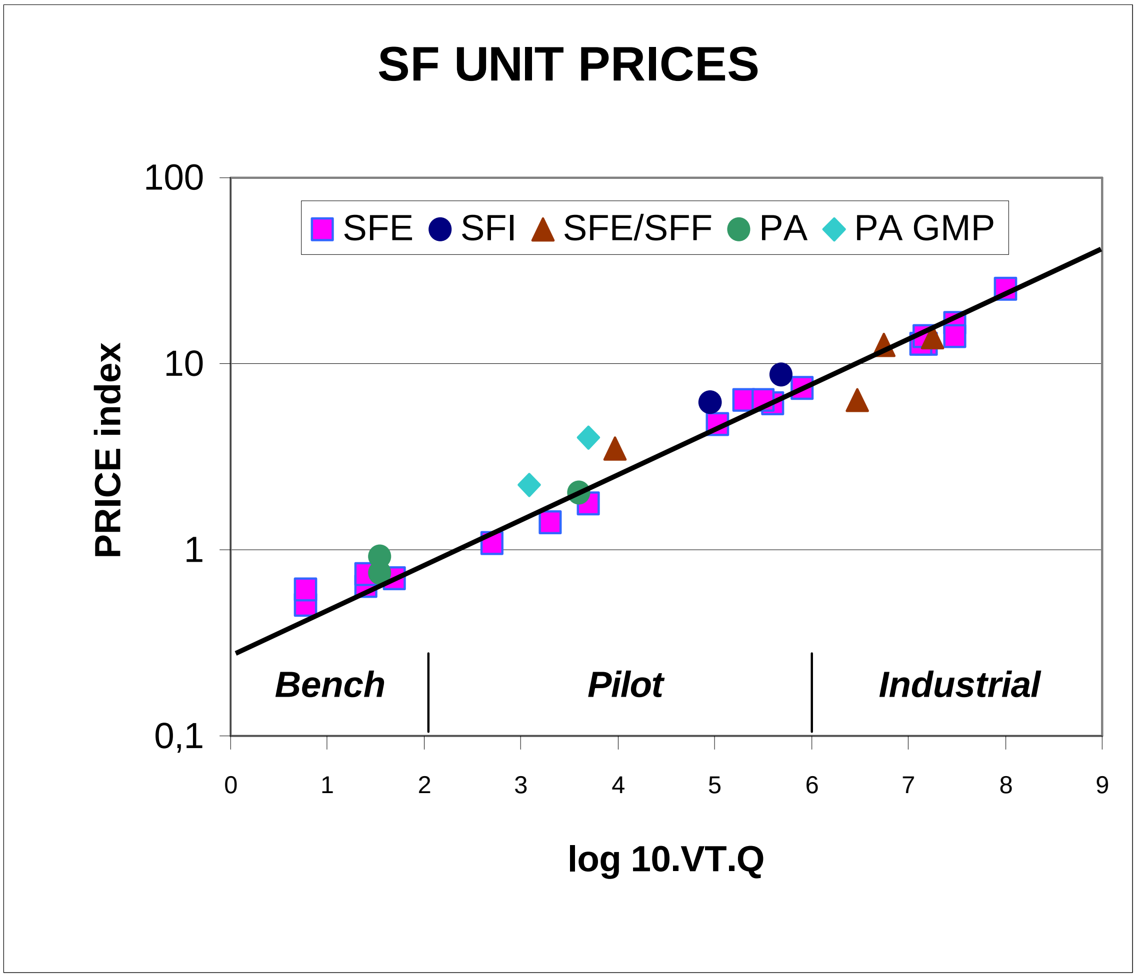


Figure 1

….but relatively low operating costs :

The most important operating cost of SFE is often manpower, except for very large units (coffee, tea, hops,…), as raw and spent material handling cannot be totally automated ; generally, two persons are required when the unit is running ; however, when long-duration batches are required, it is possible to avoid manpower operation during night, leading to important savings. The manpower cost is lower for SFF as it can be operated on continuous mode without permanent survey. Anyway, optimization of the unit design must take into account the manpower cost depending on local considerations and batch duration.

Cleaning is one of the most important time-consuming operations that is frequently underestimated during cost estimation on a large-scale flexible (multi-purpose) unit. It is extremely important to consider the cleaning issue at the very beginning of any SF equipment design, especially – but not only – for those dedicated to food or pharmaceutical products : This shall influence many choices so as to avoid piping/instruments dead-ends and all zones that could not be swept easily by the process 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.

The variable costs gather energy and fluids (carbon dioxide and co-solvent when required). On small and medium-scale units, energy is not so expensive, especially when heat is supplied by steam available on site or hot water heated by fuel or gas ; electrical heating is the most flexible but should be limited to small-scale units. Regarding CO_2 consumption of SFE units, it is mainly due to extractor depressurization at the end of extraction cycle : At first, the fluid is recycled until the pressure reaches the CO_2 reservoir pressure (~45 bar) ; then the fluid is vented to atmosphere, leading to a loss of a mass (in kg of CO_2) approximately equal to 120.V (V in m^3). In areas where CO_2 is expensive and for very large-scale units ($V_T > 1m^3$), it may be valuable to use a recompression unit to recover this carbon dioxide and recycle it. Regarding SFF, CO_2 consumption is mainly related to entrainment in extract and raffinate ; according to SEPAREX technology, both streams are depressurized step-by-step with recycling of CO_2 after a first depressurization step at ~50 bar ; this dramatically reduces CO_2 consumption that can be evaluated at ~0.1 kg per kg of feed processed in the unit. It is to be noticed that, for both SFE and SFF, the variable costs are significantly increased when a co-solvent is required, due to co-solvent losses and co-solvent recovery from spent material or raffinate and extracts.

Maintenance cost shall not be under-estimated ! Industrial production on a high pressure equipment requires a high reliability with drastic safety requirements as hazards must be eliminated : This requires a **preventative** maintenance as many parts must be inspected and 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. Preventative maintenance and inspection 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 solvent leakage) and baskets (external gaskets to avoid solvent by-pass ; sintered disks to detect deformation prior to rupture due to plugging). 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.

I would also stress on the fact that maintenance is greatly eased when a great attention is paid to a few “details” : Raw material granulometry is a basic requirement for reliable operation of SFE, as presence of fine particles may plug the basket sintered disks that will subsequently deform or even rupture, causing powder entrainment throughout the plant ; on the other hand, a performant extract-solvent separation is necessary to avoid entrainment of some fraction of extract (or powder in PA units) through the fluid recycle loop ; finally, an efficient cleaning should be frequently operated to eliminate cumulative deposition in the piping and instruments.

Most people believe that Supercritical fluid technology is very expensive due to very high investment costs in comparison with classical low-pressure equipment, and , even if it leads to high-quality products, should be restricted to high-added value products. Yet, this is far from true when very large volumes of materials are treated, as in the case of coffee/tea and hops processing, paint manufacture, soil remediation and waste treatment ! I will try to give **cost estimation** for the various types of applications, based on our experience of equipment supplier and SF plant operators.

These estimated operating costs include return-on-capital, for large-scale units :

- Food ingredients : 1-10 €/kg
- Metallurgical/Mechanical waste recycle : 0.3-1 €/kg
- Polymer/Paints Powders : 1- 5 €/kg
- Aerogels drying : 2-10 €/kg

…but also

- Pharmaceutical powder : 100-2,000+ €/kg

Conclusion :

Although extensive R&D investigations have been carried out worldwide for more than twenty-five years, it is disappointing that Supercritical Fluid applications have been still limited to few areas. However, this should not lead to give up the numerous opportunities coming up now, from food ingredients and nutraceuticals to pharmaceuticals, from biological applications and pollution abatement to new materials manufacture. As for many new technologies, probably too optimistic forecasts and uncontrolled technical announcements have rendered potential users rather skeptical after having been promised so attractive solutions… far from economic feasibility ! May I repeat once more that supercritical fluid processes are not always the best answers, but should be considered as alternatives among others, with their own advantages and limitations.

For me, it is both false to underestimate the final operating cost - as promised by some inexperienced workers on the field - and to overestimate it as this high-pressure technology continues to appear "exotic" to many engineers. As demonstrated here before, large capacity plants, with optimized design and operation, lead to prices that are very often, and surprisingly for many people, of the same order of magnitude as those related to "classical" processes submitted to similar constraints in terms of environment and consumer protection. Moreover, there are also cases where SF permit to make products or operations that cannot be realized by any other means, especially in the promising field of pharmaceuticals.

References

[1] STAHL E., QUIRIN K.-W., GERARD D., "Dense Gases for Extraction and Refining", Springer-Verlag, ISBN 0-387-18158-X, 1987.

[2] "Supercritical fluid processing of Food and Biomaterials", Edt. RIZVI S.S.H., Blackie A&P, ISBN 0-7514-0184-6, 1994.

[3] "Extraction of natural products using near-critical solvents", Edts. KING M. B. & T. R., Blackie A&P, ISBN 0-7514-0069-6, 1993.

[4] Proceedings of the 5th Meeting on Supercritical Fluids, NICE, 23-25 march 1998, Edts.PERRUT M. & SUBRA P., ISBN 2-905-267-28-3.

[5] Proceedings of the 6th Meeting on Supercritical Fluids, NOTTINGHAM, 10-13 april 1999, Edts.POLIAKOFF M., GEORGE M.W., HOWDLE S.M., ISBN 2-905-267-30-5.

[6] Proceedings of the 7th Meeting on Supercritical Fluids, ANTIBES, 6-8 december 2000, Edts.PERRUT M. & REVERCHON E., ISBN 2-905-267-33-10.

[7] BRUNNER G., "Gas Extraction", Springer, ISBN 0-387-914773, 1994.

[8] MINDER, B. ; MALLAT, T. ; BAIKER, A. ; in "High Pressure Chemical Engineering", Ed. P.R. Von ROHR, CH. TREPP, Elsevier Science, 1996, 139-144.

[9] MANDEL, F.S. ; Proceed. 4th Int. Symp. on Supercritical Fluids ; Sendai 1997, Ed. SAITO, S. ; ARAI, K. ; 493-497.

[10] UNION CARBIDE Patents:
Eur.Pat. : 0 388 915, 1990 - 0 676 547, 1992 - 0 590 647, 1993
US Pat. : 5 057 342, 1991 - 5 066 522, 1991 - 5 290 603, 1992 - 5 290 604, 1992.

[11] NORDSON Corp. Patents : Eur. Pat. : 0 421 796, 1990 - 0 520 728, 1992 - 0 595 521, 1993.

[12] PERRUT, M. ; Atti del III Congresso "I fluidi supercritici et le loro applicazioni" Grignano, ed. KIKIC, I. ; ALESSI, P. ; 1995**,** 13-17.

[13] KLEINTJENS, L.A. ; Proceed. Second Symp. on "High Pressure Chemical Engineering", Erlangen, Sept. 1990, 201-204.

[14] ADSCHIRI, T. ; KANAZAWA, K. ; ARAI, K. ; J. of Amer Ceramics Soc., 75, 1992, 1019-1022 and 2615-18.

[15] LEFEVRE, A. ; ZWAIDI, L. ; CHHOR, K. ; BOCQUET, J.F. ; POMMIER, C. ; Proceed. 3rd Int. Symp. on Supercritical Fluids, Strasbourg **1994**, Ed. BRUNNER, G. ; PERRUT, M. ; Tome 3, 309-314.

[16] HAKUTA, Y. ; TERAYAMA, H. ; ONA, S. ; ADSCHIRI, T. ; ARAI, K. ; Proceed. 4th Int. Symp. on Supercritical Fluids ; Sendai 1997, Ed. SAITO, S. ; ARAI, K. ; 255-258.

[17] Several contributions in "Proceedings of the 6th Meeting on Supercritical Fluids", NOTTINGHAM, 10-13 april 1999, Edts.POLIAKOFF M., GEORGE M.W., HOWDLE S.M., ISBN 2-905-267-30-5, 421-484.

[18] Several contributions in "Proceedings of the 7th Meeting on Supercritical Fluids, ANTIBES", 6-8 december 2000, Edts.PERRUT M. & REVERCHON E., ISBN 2-905-267-33-10, 505-536.

[19] PERRUT, V. ; PERRUT, M. ; VANDENBURG, H. ; BARTLE, K. ; Proceedings of the 7th Meeting on Supercritical Fluids, ANTIBES, 6-8 december 2000, Edts.PERRUT M. & REVERCHON E., ISBN 2-905-267-33-10, 409-414.

[20] WAGNER, R.A. ; KRUKONIS, U.J. ; COFFEY, M.P. ; Mat. Res. Soc. Symp. Ser., 121, 1988, 711-716.

[21] MARTINI-VVEDINSKY, J.E. ; SUH, N.P. ; WALDAME, F.A. ; US Patent 4,473,665, 1984.

[22] BALDWIN, D.F. ; CHA, S.W. ; PARK, C.B. ; SUH, N.P. ; US Pat. US 5 158 986, 1991, World Pat. WO 92/17533, 1992.

[23] RIZVI, S.S.H. ; MULVANEY, S. ; World Patent WO 93/06731, 1993.

[24] TEICHNER, J.J. ; NICOLAON, G.A. ; VICARINI, M.A. ; GARDES, G.E.E. ; Advances in Colloid and Interface Science 5, 1976, 245-273.

[25] AYEN, R.J. , IACOBUCCI, P.A. ; Reviews in Chemical Engineering 5, 1988, 157-198.

[26] ELALOUI, E. ; BEGAG, R. ; DURANT, M. ; CHEVALIER, B. ; ACHARD, P. ; Eur. Patent 0752389, 1997.

[27] ELLIOT, J.R. ; SRINIVASAN, G. ; DHANUKA, M. ; AKHAURY, R. ; US Pat. US 5 252 620, 1992.

[28] PEKALA, R.W. ; US Patent 5,476 878, 1995.

[29] RIGACCI, A. ; Proceedings of the 7th Meeting on Supercritical Fluids, ANTIBES, 6-8 december 2000, Edts.PERRUT M. & REVERCHON E., ISBN 2-905-267-33-10, 205-210.

[30] JUNG, J. ; PERRUT, M. ; J. of Supercritical fluids, 2001.

[31] TOM, J.W. ; DEBENEDETTI, P.G. ; Proceed. Second Int. Symp. on Supercritical Fluids, Boston 1991, ed. Mc HUGH, M. ; 229-232.

[32] TOM, J.W. ; DEBENEDETTI, P.G. ; ACS Symp. Ser. "Supercritical Fluid Engineering Science", 1993, 238-257.

[33] GALLAGHER, R.M. ; COFFEY, M.P. ; KRUKONIS, V.J. ; HILLSTROM, W.W. ; The J. of Supercritical Fluids, 5, 1992, 130-142.

[34] REVERCHON, E. ; Journal of Supercritical Fluids, vol. 10, 1997,1-37.

[35] REVERCHON, E. ; PERRUT, M. ; Proceedings of the 7th Meeting on Supercritical Fluids, ANTIBES, 6-8 december 2000, Edts.PERRUT M. & REVERCHON E., ISBN 2-905-267-33-10, 3-20.

[36] DIXON, D.J. ; JOHNSTON, K.P. ; BODMEIER, R.A. ; AICHE J., 39, 1993, 127-139.

[37] JOHNSTON, K.P. ; LUNA-BARCENAS, G. ; DIXON D.J. ; MAWSON, S. ; Proceed. 3rd Int. Symp. on Supercritical Fluids, Strasbourg 1994, Ed. BRUNNER, G. ; PERRUT, M. ; Tome 3, 359-364.

[38] NOVAK, Z. ; SENVAR-BOZIC, P. ; RIZNER, A. ; KNEZ, Z. ; Atti del III Congresso "I fluidi Supercritici e le loro applicazioni" Grignano, 1995, ed. KIKIC, I. ; ALESSI, P. ; 231-238.

[39] FREDERIKSEN, L. ; ANTON, K. ; BARRATT, B.J. ; VAN HOOGEVEST, P. ; LEUENBERG, H. ; Proceed. 3rd Int. Symp. on Supercritical Fluids, Strasbourg 1994, Ed. BRUNNER, G. ; PERRUT, M. ; Tome 3, 235-240.

[40] BENOIT, J.P. ; ROLLAND, H. ; THIES, C. ; VAN DE VELDE, V. ; Patent EP 0 706 821, 1996, WO96/11055, 1996, US 6,087,003, 2000.

[41] WARD, D. , SUNOL, A.K. ; CURCIO, R. ; Proceed. Second Int. Symp. on Supercritical Fluids, Boston 1991, ed. Mc HUGH, M. ; 364-367.

[42] 3M, US Pat. 5,340,614, 1994 ; World Pat. 94/18264, 1994.

[43] GREINER, R.W. ; Eur. Pat. 0 405 284, 1991.

[44] BERNEBURG, P.L. ; KRUKONIS, V.J. ; US Pat. 5,035,921, 1991.

[45] FRANÇAIS, E. ; MAJEWSKI, W.; PERRUT, M. ; BRANDT, A.C. ; Proceed. 4th Int. Symp. on Supercritical Fluids ; Sendai 1997, Ed. SAITO, S. ; ARAI, K., 243-246.

[46] MAJEWSKI, W. ; PERRUT, M. ; Proceedings of the 7th Meeting on Supercritical Fluids, ANTIBES, 6-8 december 2000, Edts.PERRUT M. & REVERCHON E., ISBN 2-905-267-33-10, 779-780.

[47] ECKARDI, C. ; SCHLENKER, W. ; WERTHEMANN, D. ; (CIBA), Brev. Eur. EP 0 543 779, 1991.

[48] KNITTEL, D. ; SCHOLLMEYER, E. ; BENKEN, R. ; BUSCHMANN, H.J. ; SAUS, W. ; (JAPER) , Germ. Pat. DE 42 00352, 1992, World Pat. WO 93/14259, 1993.

[49] TRUCKEN-MUELLER, K. ; WOERNER, G. ; Germ. Pat. DE 42 00498, **1992**, World Pat. WO 93/14255, 1993.

[50] PERRUT, M., Proceed. 4th meeting "Supercritical Fluids and Environment",VILLEURBANNE, Ed. ISASF, 1997, 1-10.

[51] ECKERT, C.A. ; CHANDLER, K. ; Proceed. 4th Int. Symp. on Supercritical Fluids ; Sendai 1997, Ed. SAITO, S. ; ARAI, K. ; 799-806.

[52] KENDALL, J.L. ; DE SIMONE, J.M. ; Proceed. 4th Int. Symp. on Supercritical Fluids ; Sendai 1997, Ed. SAITO, S. ; ARAI, K. ; 771-776.

[53] MAJEWSKI, W. ; PERRUT, M. ; Proceedings of the 7th Meeting on Supercritical Fluids, ANTIBES, 6-8 december 2000, Edts.PERRUT M. & REVERCHON E., ISBN 2-905-267-33-10, 723-730.

[54] HARROD, M. ; MACHER, M.-B. ; Van Den HARK, S. ; Moller, P. ; Proceedings of the 6th Meeting on Supercritical Fluids, NOTTINGHAM, 10-13 april 1999, Edts.POLIAKOFF M., GEORGE M.W., HOWDLE S.M., ISBN 2-905-267-30-5, 253-258.

[55] CASTOR, T.P. ; HONG, G.T. ; World Patent WO 91/01367, 1991.

[56] CASTOR, T.P. ; HONG, G.T. ; Proceed. Second Int. Symp. on Supercritical Fluids, BOSTON, Ed. M.McHUGH, 1991, 139-142.

[57] PILZ, V. ; RUPP, R. ; US Patent 4,263,253, 1981.

[58] KAMIHIRA, M. ; TANIGUCHI, M. ; KOBAYASHI, T; ; Agric. Biol. Chem., 51, 1987, 407-412.

[59] WEI, C.I. ; BALABAN, M.O. ; FERNANDO, S.Y. ; PEPLOW, A.J. ; J. of Food Protection, 54, 1991, 189-193.

[60] "High Pressure and Biotechnology", Ed. BALNY, C. ; HAYASHI, R. ; HEREMANS, K. ; MASSON, P. ; Colloque INSERM N° 224, John Libbey ISBN 2-85598-512-9, 1992.

[61] SMELT, J.P.P.M. ; RIJKE, G.G.F. ; "High Pressure and Biotechnology", Ed. BALNY, C. ; HAYASHI, R. ; HEREMANS, K. ; MASSON, P. ; Colloque INSERM N° 224, John Libbey ISBN 2-85598-512-9, 199**2**, 361-364.

[62] CASTOR, T.P. ; LANDER, A.D. ; World Patent WO 93/17724, 1993.

[63] BURNOUF, T. ; BURNOUF, M. ; BOUZIDI, A. ; PERRUT, M. ; World Patent WO 94/03590, 1994.

[64] BOUZIDI, A. ; PERRUT, M. ; MAJEWSKI, W. ; Proceed. 4th Int. Symp. on Supercritical Fluids, Sendaï, Ed. S. SAITO, D. ARAI, 1997, Vol A, 387-390.

[65] FAGES, J. ; MATHON, D. ; POIRIER, B. ; AUTEFAGE, A. ; LARZUL, D. ; JEAN, E. ; FRAYSSINET, P., Proceed. 4th Int. Symp. on Supercritical Fluids ; Sendai 1997, Ed. SAITO, S. ; ARAI, K. ; 383-386.