General rules for Extrapolation from Pilot Plant to Industrial Scale SFE or SFF :

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Introduction :

Extrapolation of experimental results obtained at lab and/or pilot scale to production equipments is a major challenge for chemical engineers, especially when new technologies are developed, as it is the case for supercritical fluid applications for which very few results have ever been published.
Illustrated by problems met on various processes including solid extraction and liquid fractionation, we present some rules that could be followed during design, operation, maintenance and cleaning of large-scale plants using supercritical carbon dioxide and co-solvents.

Design of large-scale units :

Basic chemical engineering for supercritical fluid equipment design can be found in a recent book by BRUNNER[1], but few data are presently available for calculation of main equipments to be assembled into large scale SF plants :

Heat exchangers

Double-tube counter-current heat exchangers are used on pilot and semi-industrial plants but cannot be used on units where the SF flowrate exceeds 1,000 $kg.h^{-1}$: shell-and-tube heat exchangers are required for providing a sufficient transfer area. According to our experience, we recommend :

- Obviously, process fluid always on tube side and heating/cooling medium on shell-side ;
- Horizontal SF heater (when SF is pumped in liquid phase) or cooler (when SF is compressed in a gas phase), after SF pump/compressor, with one pass on shell-side and two passes on tube side, U-tubes being acceptable as the SF is clean at that point ;
- 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 condensor (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.

Extraction autoclaves

Most attention is paid to closure systems permitting a fast and easy opening/closure, as solid extraction 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** passive safety blocking the closure systems when some pressure remains inside the autoclave.

Fluid compression

Two possible fluid cycles can be used :

- Liquefied gas pumping : in most small and medium scale equipments, a volumetric high pressure pump is used to compress the fluid in liquid phase ; generally, membrane pumps are preferred for flowrates up to 1,000 kg/h meanwhile piston-plunger pumps are used for larger capacities where they are much less expensive than the precedent type. It is important to notice that these pumps have check-valves presenting a significant pressure drop at full capacity : this requires a sub-cooling of the liquefied gas of at least 3°C below the boiling temperature at the inlet pressure (~40 to 50 bar in most cases) to avoid cavitation in the pump head that must also be cooled.

However, it happens in some processes that the extract-fluid separation is not performed by depressurization below the critical pressure, but by temperature change or fluid scrubbing or adsorption, as it is performed in the very large scale decaffeination plants : the total pressure drop being small, centrifugal pumps can be used, delivering very large flowrates (higher than 20,000 kg/h) at a much lower cost than any volumetric pump.

- Gas compression : Instead of liquefying the gas prior to pumping it in liquid phase, it is also possible to compress it as a 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 condensor are required. Moreover, some problems may occur if the extract-fluid separation is not total, especially if waxy materials are entrained in the gas phase to the compressor.

Operation of large-scale units

Solid extraction processes (SFE)

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

- Fine particles migration and plugging may cause basket sintered disk deformation ; this is the most widely encountered problem as most operators do not take enough care to the raw material granulometry during grinding ; We strongly recommend to avoid very fine particles by grinding monitoring and/or screening the raw materials prior to filling the baskets ; a paper filter may be an aid in certain cases to prevent this problem. In other cases, the raw material may agglomerate in form at a thick “cake”, what drastically reduces the SF-material contact and extraction efficiency ; this may also lead to total plugging of the basket and deformation of the sintered disks. When such “sticking” materials are processed, a pelletization step is required, as for hops treatment. When pelletization is not available, we can recommend to blend the raw material powder with an inert granular material that will prevent this agglomeration.

In the worst case, basket disk plugging may lead to basket deformation and blockage inside the extraction autoclave, causing important 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 with SF flow stop when it reaches a value that indicates such plugging, below the pressure drop that irreversibly damage 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 SF by-pass between the basket and autoclave

walls when the external gasket of the basket is not totally efficient to force SF to percolate through the basket. With certain autoclave lid designs, such damage may cause a leakage to atmosphere when the rays appear on the zone of main gasket ; so we believe it is important to operate with adequate means of basket handling and careful manpower.

Supercritical Fluid Fractionation (SFF) :
In most cases, SFF is much easier to operate than SFE as pressure vessels are not often opened and closed. However, column packing plugging may happen and lead to flooding : it is generally a slow process with deposition of a solid or highly viscous material onto the packing, that progressively reduces the open section of the column and creates zones no longer swept by the fluid, what generally "catalyses" the deposition, until the moment where brutally flooding appears, requiring operation stop and unit 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 pretreat the feed (filtration, …), to change the operating conditions (possibly increased temperature) or to operate preventative column cleaning regularly.

SF recycle loop
For all industrial-scale processes, SF is recycled for obvious economical and ecological reasons. This means that the separation of the extract from the fluid prior to its recycling must be as perfect as possible to avoid extract deposition throughout the recycle loop, especially the colder parts (condensor and sub-cooler, liquefied gas reservoir, or compressor), 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 (inert gases, pollutants,...).

Maintenance of large-scale units

Industrial production with supercritical fluids requires a high reliability operation of high pressure equipments 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. This 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 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, I would stress on the fact that maintenance is greatly eased when a great attention is paid to extract-solvent separation to avoid entrainment of some fraction of extract through the fluid recycle loop, and if an efficient cleaning is frequently operated.

Cleaning large-scale units

One of the most important issue for operating a supercritical fluid process on a large-scale flexible unit is probably ***cleaning***, especially when food or pharmaceutical products are treated. Obviously, it is much more difficult for pharmaceutical processing than for foodstuffs and we will focus our attention here on those pharmaceutical products, as it is clear that drastic simplifications of this procedures can be accepted for foodstuffs processing, happily ! It can also be considered that less strict requirements are imposed for phytopharmaceuticals than for synthetic drugs in their final form.

For pharmaceutical processing, it has to be proved that no contamination by previously processed compounds may occur ; but according to GMP (pharmaceuticals) even when the plant is dedicated to only one product, it is also required to avoid cross-contamination from one lot to the other. Although cleaning is always an issue on any type of process and equipment operated in GMP, it is much more severe for supercritical fluid process and equipment as the operator must ***prove*** that the equipment is cleaned rid of previous compounds ; this constraint is generally matched by the famous "***swab***" technique consisting in scrubbing the equipment wall with a specific swab that is further extracted with a solvent which is evaporated, leaving a dry residue easy to weigh and analyze. In the special case of SF equipment, most parts cannot be opened between each lot manufacture and the swab technique cannot be used. Moreover, as most high pressure parts - like valves - are not Clean-In-Place (CIP), cleaning procedure validation is really a troublesome burden !

According to our experience, we are convinced that the only GMP-acceptable cleaning technique requires :

- Between batches :

Rinsing the whole unit with an adequate liquid solvent , dismantling and cleaning dead-ends, rinsing again with the liquid solvent, with sampling for cleaning validation, drying with gaseous nitrogen or CO_2 to eliminate solvent vapor and rinsing with liquid/supercritical CO_2 that is finally vented to atmosphere in order to eliminate most extracted impurities, (mainly liquid solvent) ;

- Between different products :

Total or partly dismantling of the equipment, cleaning of each part, swabbing the pressure vessels, …, reassembling the equipment, rinsing with an adequate liquid solvent with sampling for cleaning validation, drying with gaseous nitrogen or CO_2 to eliminate solvent vapor and rinsing with liquid/supercritical CO_2 that is finally vented to atmosphere in order to eliminate most extracted impurities, (mainly liquid solvent) ;

Cleaning validation is obtained through liquid solvent samples analyses (dry weight of residue and residue identification are the key-parameters) and swab characterization according to the classical technique.

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.

Extrapolation from Pilot Plant to Industrial Scale SFE : a Case Study

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Introduction

In order to apply Supercritical Fluid Extraction processes at large scale, technical and economical extrapolation methods have been developed. These methods are dependent of the nature of the extraction and are based on experimental results obtained on pilot plant units. We describe here a general extrapolation procedure, and a case study is presented to illustrate an economical estimation of a supercritical fluid extraction.

Technical Design of an Industrial Plant

The objective of this design is to determine operating conditions (pressure, temperature), but also what will be the optimal configuration of the plant, the dimension and the number of extractors, the capacity of the pump...
The design will always require some experimental data that have to be determined on a pilot plant unit.
The procedure of this design will be :
- to determine first the optimal physical conditions through a scanning of different pressures, temperatures, solvents... .
- to obtain thermodynamic and kinetic data to design the industrial plant.

The extrapolation method will depend on the nature of the extraction and particularly on the mechanism controlling the extraction. Several mechanisms can be found :
- Some extractions are only limited by the solubility of the extract in the fluid. This is the case of the extraction of lipids when the access to the extract in the matrix is easy. This is for instance the case of extraction of beef tallow [1] or the extraction of fats from butter or cheese.
- Some extractions are only limited by diffusion and especially the internal diffusion. In certain cases like basil oil extraction or ginger extraction, the solubility of the extract in supercritical fluid is very high but the access in the matrix is more difficult, so that the concentration of extract in the solvent is far below the solubility. In this case, the extraction can be represented only by diffusion and kinetic parameters [2,3].
- Most of the extractions are more complex and are limited by both solubility and diffusion. In a lot of cases, a fraction of the extract is extracted first and the extraction rate is function of the solubility of the extract in the fluid. The rest of the extract is extracted afterwards and the extraction is limited by diffusion [4,5]. This is the case in a lot of natural products extraction from seeds, as shown on figure 1 for spices extraction [7] :

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_2 saturation at the autoclave exit, the slope **a** being the extracts solubility in CO_2 in these extraction conditions.
It is remarkable to see on figure 1 that 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_2 to feed ratio), even for very different values of **a**.

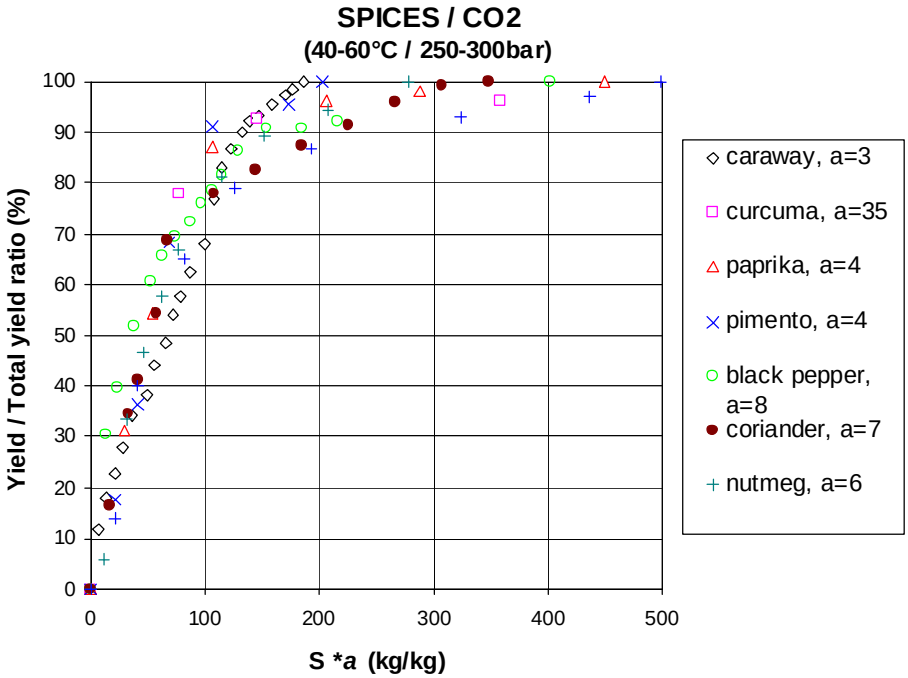

Figure 1. Spices extraction by supercritical CO_2 [7]

It is to be noticed that the amount of "free" extract is usually dependent on the granulometry of the crushed seeds.

When several compounds can be extracted, the rate of extraction and the mechanism of extraction can be different for each of them.

Depending on the complexity and on the nature of the extraction, different extrapolation methods are available to design the production unit :

- A very simple way to extrapolate the experimental data obtained on a pilot plant is to keep the ratios U_s/M_f and M_s/M_f constant. (U_s is the solvent flowrate (in $kg.h^{-1}$)), M_f is the feed mass in the extractor (kg), and M_s is the solvent mass required for the extraction (kg).
The ratio U_s/M_f is inversely proportional to residence time of the eluent in the extractor t_r (see equation 1), and this ratio will have to be conserved, especially for extraction limited by internal diffusion. These extractions are almost not dependent on the solvent flowrate, but the "contacting" time of the feed with the solvent is the determinant factor of plant design. Therefore, it will be necessary to use very large extractors or to use several extractors in series in

order to maximize the contacting time of the solvent with the feed. On the other hand, it is possible to minimize the solvent flowrate and the energy consumption of the plant.

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

with : ε : Void fraction of the bed
ρ_s : Specific gravity of the solvent
ρ_f : Specific gravity of the feed
M_f: Feed mass
U_s : Solvent flowrate

The ratio M_s/M_f corresponds to the amount of solvent needed to extract one kilogram of the feed. This ratio has to be maintained in the case of extraction limited by the solubility of the extract or by the thermodynamical equilibrium between the feed and the eluent. In these extraction the amount of solvent is the determinant factor of the plant design. 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.

- In complex extractions, when both diffusion and thermodynamic are linked, or when the extract is a complex mixture of several components recovered at different rates, a numerical simulation software of the extraction can be very useful to estimate quickly any configuration and to optimize more precisely the industrial plant. A lot of different models have been proposed in the literature, and we built a versatile simulation software allowing to represent a lot of different systems [6].

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 discharged of solvent, the feed is replaced and the extractor is recompressed, when the other one is used for extraction. Three or more extractor configurations are often designed in order to optimize the extraction plant. One extractor is discharged and loaded when the others are operated in extraction. These extractors are connected in series, so that the feed and the solvent are contacted counter-currently. The last extractor of the series is the one with the previously unextracted feed and the first extractor of the series is the one which has been contacted the longest time with the eluent, and the next to be discharged. This "carrousel" implementation allows most of the time to reduce the amount of CO_2 required for a given extraction, and therefore, to reduce the energy consumption of the production plant. For a given production capacity, increasing the number of extractors will therefore decrease the energy consumption and the operating costs, but increase most of the time the investment costs, depending on the capacity of the extractors. The extractor volume will depend on the number of shift/day that can be operated. The more important is the number of shift/day, the less is the volume of the

extractors, and the less is the investment cost. The economic estimation allows in each case to decide of the optimal configuration.

Economical estimation of an industrial plant

The extraction of an economically interesting oil obtained from a natural seed is chosen to illustrate this estimation.

The characteristics of the raw material are the followings :
- Granulometry of the seed : 0.5 - 1.5 mm
- Moisture of the seed : ≈ 8%
- Apparent specific gravity : 550 $kg.m^{-3}$
- Lipid in the feed : 3.8 % w/w

The extraction is performed at 250 bar and 40°C. The extract is recovered in 3 decompression/heating steps until 45 bar and 30°C.
Figure 2 represents 3 extractions curves obtained on a pilot plant at different flowrates Us. The extractor volume is 1.5 l.

At the beginning of the runs, the extraction rate is approximately proportional to the amount of CO_2 pumped through the extractor, whatever the flowrate: the concentration of the extract in the fluid is therefore equal to the solubility which is in this case 0.9 $g.kg^{-1}$. At the end of the runs, the extraction is limited by diffusion, mainly inside the particles.

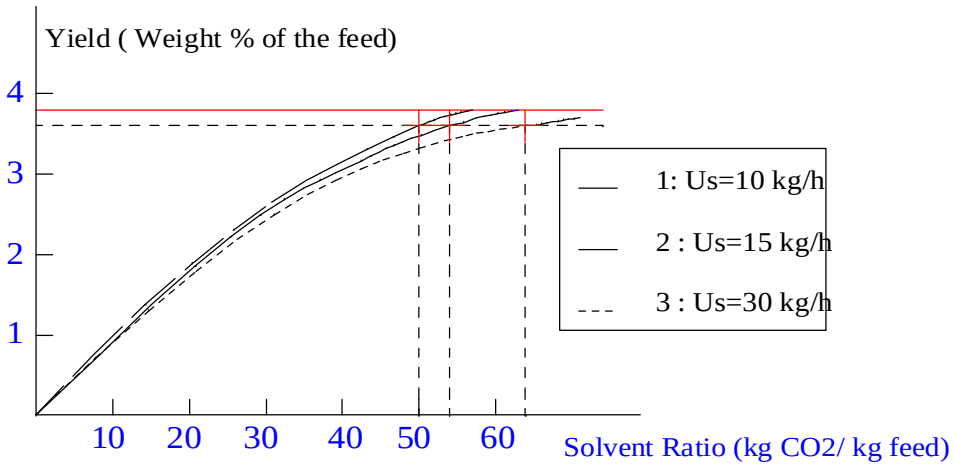

Figure 2 Extraction curves at different solvent flowrates

The industrial requirements are :

- A recovery yield of 95 % of the total extract (3.6% of the total mass)
- 2 capacities will be considered :
  - case a) 7 000 kg extract / year
  - case b) 10 700 kg extract /year

In case a) the plant will work 108 h/week and 48 weeks /year (5 200 h/year) with 3 operators working 3 x 8 h.
In case b) the plant will work 8 000 h/year with 4 operators working 4 x 8 h.
In both cases, the amount of seed to be treated is 37.1 $kg.h^{-1}$.

The economic calculation will be done in a 2-extractor configuration, one being in extraction mode while the other one is discharged, loaded, and compressed.

The extrapolation method consists here in keeping the ratios U_s/M_c and M_s/M_c constant. Table 1 presents the extrapolation of the 3 curves obtained on the pilot plant.

Extraction	Batch length (h)	U_s/M_c	M_s/M_c	M_c (kg)	U_s ($kg.h^{-1}$)	Extractor Volume (l)
1	4	12.5	50	160	2000	291
2	2.9	18.75	54	115	2160	209
3	1.7	37.5	64	68	2560	124

The economic estimation allows to decide which case is the most appropriate. The estimation in case 2 is detailed below.

Determination of production costs

Energy :
The CO_2 energy cycle encloses :
Pumping from liquid state 45 bar, 5°C to supercritical fluid 250 bar, 40°C : ΔH=14 $kcal.kg^{-1}$
Expansion : from 250 bar, 40°C to 45 bar , 30 °C in three steps : ΔH= 46 $kcal.kg^{-1}$
Condensation : at 45 bar from 30°C to 5 °C : ΔH= 60 $kcal.kg^{-1}$

- Cooling utilities design :
60 kcal / kg CO_2 that is to say 130 000 kcal/h are required. In the case of an air refrigerated cooling device, the power of the cooling machine will be twice the required power. A buffer reservoir will be used to store the cooling glycol/water mixture and two pumps will pump the mixture to the process and to the cooling machine. The energy consumption of this system is evaluated at 120 kWh.

- Hot utilities design:
A gas boiler is recommended. It provides hot water at 85 °C stored in a buffer and then sent to the process. The required power is 130 kcal/h, we will therefore plan a 200 T/h boiler, and the gas energy consumption taking into account heat losses is evaluated at 150 kWh.
- Pumps : The CO_2 pump consumption is estimated at 25 kWh. The other pumps and electric devices consumption (Air compressor, utilities....) are approximated at 15 kWh.

The total energy consumption is therefore evaluated at :
Electricity : 160 kWh
Gas : 150 kWh

CO_2 consumption

The 2 principal causes of solvent consumption are :

- Extract withdrawing : The optimization of an automated extract withdrawing system and the optimization of the extractor emptying and filling, allow to minimize the solvent consumption which is estimated at 0.5 kg CO_2/ kg extract.
- Extractor emptying : At each extractor shift, a 210 l extractor is vented from 45 bar, 20°C to atmospheric pressure which corresponds to a waste of 25 kg of CO_2 / shift.

The total CO_2 consumption is therefore evaluated at

- case A : 50 T/ year
- case B : 75 T/year

Labour work :

The whole unit is automated and we evaluate the labour work at :

- 1 operator working 3 x 8 (in case A)
- 1 operator working 4 x 8 (in case B)
- 1 maintenance technician
- Supervision/Management (25%)
- 1 more operator in the day is in charge of feed reception, storage, crushing...

Global economic evaluation : (1 euro~6.6 FRF)

Investment :

Process : 6 M FRF (million of French Francs)
Utilities : 1 M FRF
Feed preparation : 1 MFRF

Total : 8 M FRF (1.21 MEuro)

Operating costs:	case A (in M FRF)	case B (in M FRF)
Labour work	1.2	2.0
Energy	0.8	1.1
Maintenance	0.2	0.2
Insurance / taxes	0.2	0.2
General costs	0.6	0.9
Total	3.0	4.4

Considering a capital return of 25%, the annual cost is evaluated at 5 M FRF/year in case A and 6.6 M FRF in case B that corresponds to 25 FRF/kg (3.8 Euro/kg) feed in case A and 22 FRF/kg (3.3 Euro/kg) feed in case B.

Conclusion

In front of the diversity and the complexity of supercritical fluid extraction, we dispose of all experimental and theoretical tools to compute and extrapolate pilot plant experimental data to an industrial unit. A lot of theoretical thermodynamic and kinetic data are now available, and experimental extractions carried out on pilot plants allow to build extrapolation models, from the very simple ones (like it is described in this case study) to the very sophisticated ones based

on a numerical simulation software and taking into account hydrodynamic, thermodynamic and kinetic phenomena.

These extrapolation methods allow to determine what will be the best operating conditions, and the optimal system configuration of the production plant from a technical and economical point view. If 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 : the optimization of the extract recovering and fractionation, the energetic process optimization, or the improvement of the extractor emptying and loading procedures are also some very important points that must be considered in the industrial process design.

References

[1] CHAO R.R. , Supercritical fluids processing of food materials Eds Rizvi, ISBN 0-7514-01846, 1994, p. 203-213
[2] REVERCHON E., SESTI OSSEO L., Proceedings of the third international symposium on supercritical fluids, ISBN 2-905267-23-8, vol 2, 1994, p.189
[3] SANKAR K.U. , Supercritical fluids processing of food materials, Ed. Rizvi, ISBN 0-7514-01846, 1994, p. 44
[4] GOTO M. , ROY B.C., NOMURA Y., HIROSE T., Proceedings of the third international symposium on supercritical fluids, ISBN 2-905267-23-8., vol 2, 1994, p. 165-170
[5] SOVOVA H. , Proceedings of the third international symposium on supercritical fluids, ISBN 2-905267-23-8, vol 2, 1994, p. 131-136
[6] CLAVIER J. Y., MAJEWSKI W., PERRUT M., Atte del III congresso i fluidi supercritici e loro applicationni, Eds. Kikic. I. and Alessi P., 1995, p 107- 116.
[7] MAJEWSKI W., Proceedings of the fifth meeting on supercritical fluids, ISBN 2-905-267-28-3, vol 2, (march 98),p. 545

CONCLUSION : FUTURE TRENDS

During the two past decades, supercritical fluid applications have been reaching commercial scale mostly for food and pharmaceutical industries through the development of extraction/fractionation processes treating **natural products**, mainly solid vegetals (coffee, hops, aromatic plants, medicinal plants) and liquids (fish oils, edible oils, essences, beverages,…). This will continue to be the main applications in the next decade :

- **Extraction** (SFE) from solid materials is now widely used for treatment of **natural products**, as food products (coffee, tea,…), food additives and supplements (aromas, colorants, vitamin-rich extracts, specific lipids, …), phytopharmaceuticals including pesticide removal from polluted raw materials like ginseng. Residual organic solvent (or other impurities) can also be removed from final products extracted by classical solvents.

- **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 ; industrial applications are now developing for aromas production from fermented and distilled beverages or essences deterpenation, fractionation of polyunsaturated fatty acids from fish or vegetal oils, recovery of active compounds from fermentation broths, ….

However, new applications are now under developments, mainly related to highly selective separation processes and material transformation :

- Sophisticated highly selective processes are used to treat some natural products like **Preparative Scale Supercritical Fluid Chromatography** (PSFC) that is under industrial development for ultimate fractionation of polyunsaturated fatty acids from fish oil ; moreover, due to the high diffusivity of supercritical fluids, they can be used as vectors for **impregnation** of aromas in food products, or pharmaceuticals into excipient matrixes or bio-devices.

- **Particle design** using supercritical fluids is subjected to extended efforts in many pharmaceutical/cosmetic companies, with several different processes, aimed to obtain free-flowing powders, or submicronic particles as needed for aerosol delivery, or microspheres/microcapsules or liposomes ; full-scale developments will probably be announced in the next months.

On the long term, I guess that supercritical fluids will be very widely used as **reaction** media, as their tunable properties are highly attractive, meanwhile their high diffusivity permits to drastically reduce the diffusion limitations of the reaction kinetics. For example, enzymatic reactions and hydrogenation (for example of unsaturated vegetal oils) are deeply investigated.

And some **biological** applications might also provide solutions to present drastic problems related to cell lysis, sterilization and virus inactivation.