CONTROLLED PRECIPITATION OF ACTIVE PHARMACEUTICAL INGREDIENTS EMPLOYING SUPERCRITICAL FLUIDS: SCALE-UP CONSIDERATIONS

Albertina Ariën[1]*, Marcus E. Brewster[1], Bruno De Witte[2]

[1] Johnson & Johnson Pharmaceutical Research and Development, Turnhoutseweg 30, B-2340 Beerse, Belgium
[2] Janssen Pharmaceutica N.V., Janssen Pharmaceuticalaan 3, 2440 Geel, Belgium
tarien@prdbe.jnj.com, phone +32 14 60 65 39, fax +32 14 60 70 83

ABSTRACT

The production process of active pharmaceutical ingredients (API) involves many unit operations at the end of the synthesis to obtain a dry pure crystalline product. Many of these steps require a significant quantity of various solvents and increase the risks of operator exposure and product contamination.

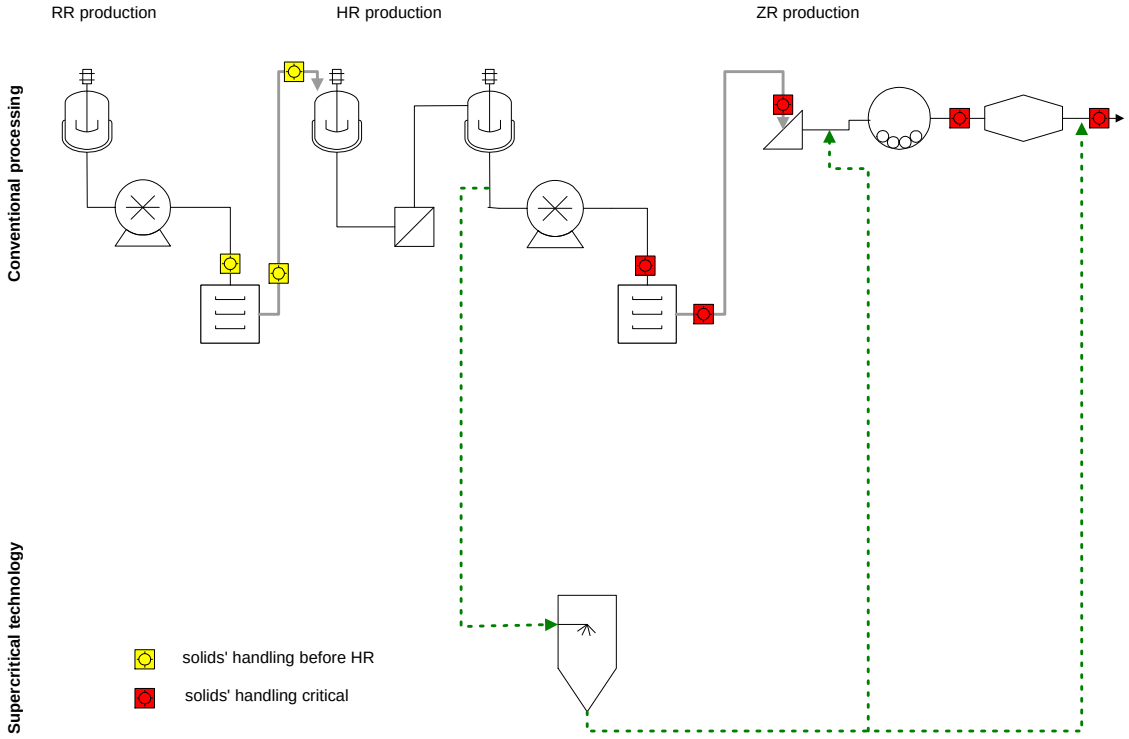
Supercritical antisolvent precipitation offers significant advantages over the traditional processes as it allows an API solution to be converted to a dry end product of specified granulometry and purity, by-passing several unit steps like cooling crystallization, centrifugation, drying and powder milling/homogenisation in one contained process.

This presentation shows the results of 2 case studies where the supercritical antisolvent process was applied. The impact of the various process parameters on the dryness, purity and crystallinity of the products was studied on a lab-scale system. From these results the economical aspect of scale-up of the SCF-process was considered and compared to conventional technologies. These results show that SCF technology is a viable technique for the production of highly potent pharmaceuticals.

INTRODUCTION

The advent of high through-put screening has led to the development of new drug candidates that tend to have poorer oral bioavailability [1]. In addition, new pharmaceutical entities are characterized by higher activity to such an extent that their viability and commercial interest is often jeopardized by the limitations of the current chemical and pharmaceutical production facilities. Indeed, the production of a new API involves many standard unit operations and powder handling steps before a dry and pure crystalline product is obtained that can be formulated into a suitable dosage form (Figure 1). In this process, risks for operator exposure and product contamination are high (red squares). In addition, solvent use (cleaning) and the corresponding environmental impact is high. One approach to reduce these risks is to combine various unit operations into one contained step by using supercritical fluids. Indeed, supercritical antisolvent precipitation has been successfully applied to the precipitation of many model API's [2]. The process is contained and offers the possibility to tune properties of the final product such as particle size, polymorphic form, purity, surface charge and dissolution properties [3-6], activities that are often split between chemical and pharmaceutical production facilities.

The aim of the current research project is to evaluate the suitability of the supercritical antisolvent precipitation process for 2 model compounds. Initial experiments are carried out on lab-scale equipment to gain insight into the process parameters that influence product stability, dryness, purity, particle morphology and product yield. These results are used to gain



insight on the economical aspects related to the scale-up of the SCF process. The economical impact of the technology will then be compared to that of the conventional technology.

Figure 1: Impact of SCF process on standard API processing.

MATERIALS AND METHODS

Model compounds A and B were provided by Janssen Pharmaceutica. All solvents were analytical grade. CO_2 (= 99.9 vol%, purity 3.0) was supplied in gas cylinders with dip tube by Messer. N_2 (= 99.999 vol%, purity 5.0) was provided in a gas cylinder by Messer.

The solubility measurements and phase behavior studies were performed in a phase equilibrium unit supplied by SITEC, Switzerland. The unit is equipped with a 50 ml view cell, a counterbalance piston and a sampling loop of 2.9 ml. Maximal working pressure and temperature are 500 bar and 120 ºC. For the phase behavior studies of the isopropanol - CO_2 and methyl-ethyl ketone (MEK) – CO_2 mixtures, the solvents were brought into the cell and heated to the working temperature. CO_2 was added via the handpump and phase behavior at various pressures was observed visually.

The solubility of the model compound A in CO_2 was determined at various pressures and temperatures (see Figure 3). The compound was mixed with CO_2 in the cell for 30 minutes at the specified pressure and temperature. Samples were taken from the fluid phase at constant pressure employing the sampling device and the counterbalance piston. The amount of drug solubilized in CO_2 was determined by UV spectroscopy after recovery of the

precipitated drug from the sampling device with an appropriate solvent (compound A: methanol; compound B: ethanol).

The precipitation of the model components out of 3 component mixtures, compound A – isopropanol – CO_2 and compound B – MEK – CO_2 was studied at various pressures and temperatures. Briefly, the compound was dissolved in the solvent and heated in the view cell to the operating temperature. Subsequently, CO_2 was added and pressure was build up. Precipitation was allowed to proceed for 30 minutes before a sample was taken from the upper fluid phase to determine the amount of drug remaining in solution after precipitation. The precipitation yield was determined as the percentage drug that precipitated of the total amount of drug that was initially placed in the cell.

The dryness, polymorphism, particle morphology and purity of the precipitated materials was analysed by gas chromatography (GC), thermogravimetry (TGA), differential scanning calorimetry (DSC), infrared analysis (IR), scanning electron microscopy (SEM) and HPLC analysis.

RESULTS AND DISCUSSION

Phase diagrams of the solvent – CO_2 mixtures were constructed to determine the miscibility of the solvent and CO_2 at varying pressures and temperatures. Figure 2A shows the phase behavior of isopropanol – CO_2 mixtures. One phase is observed at pressures above 114 – 118 bar for temperatures varying from 70 to 80 ºC. These data correlate well with literature data for 1-propanol at 61ºC [7]. Similarly, MEK - CO_2 mixtures form a single phase at 70ºC at pressures above 107 bar (Figure 2B).

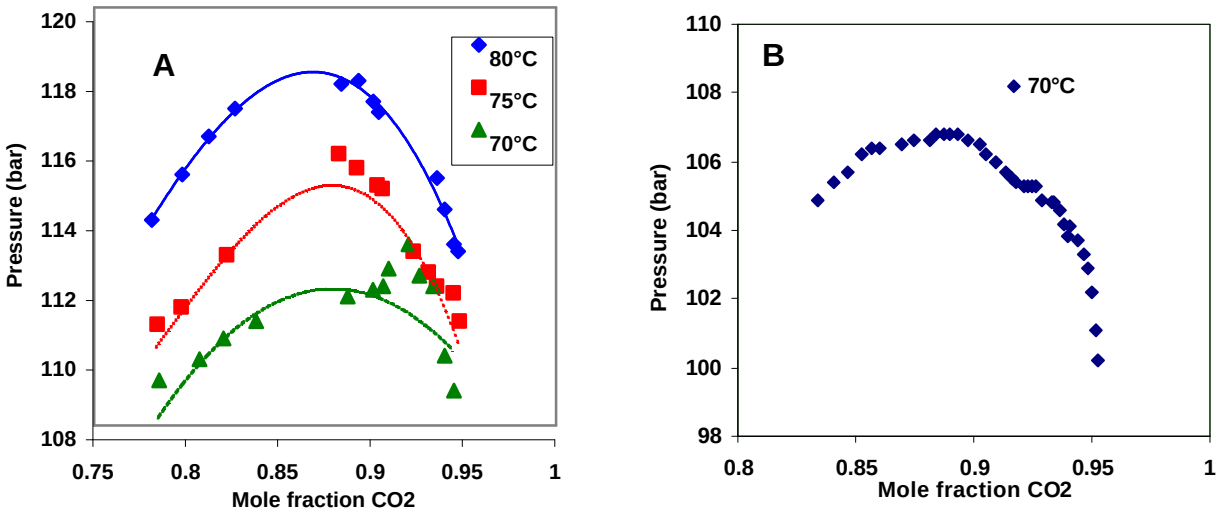


Figure 2: Phase behavior of (A) isopropanol – CO_2 mixtures at various temperatures and (B) MEK – CO_2 at 70ºC.

The solubility of compound A in CO_2 was determined as a function of pressure and temperature. Figure 3 shows that the solubility of the compound in CO_2 is poor and increases with increasing pressure and reducing temperature. This inverse temperature dependence is typical for mixtures below their cross-over point where solubility of the compound in CO_2 is controlled by the density of CO_2 rather than the vapor pressure of the compound. Results

suggest that the supercritical anti-solvent process can be used for the precipitation of the model compound. Similarly, compound B showed a poor solubility in supercritical CO_2.

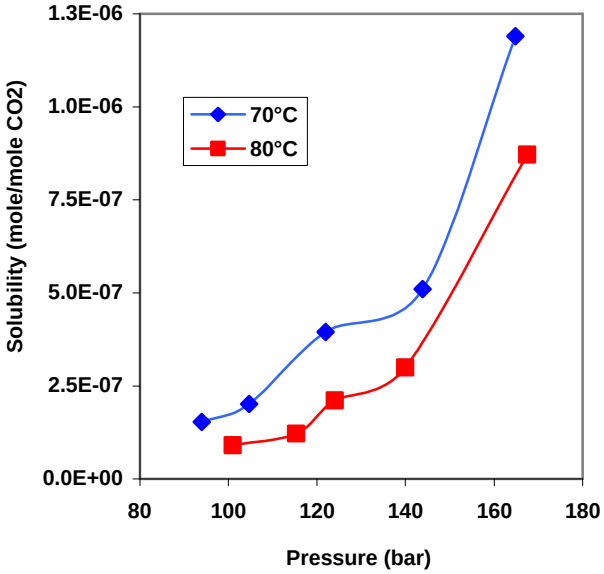


Figure 3: Solubility of compound A in CO_2 as a function of pressure and temperature.

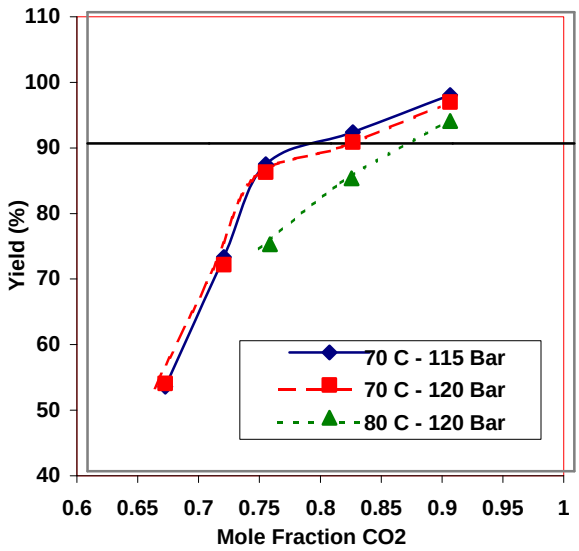


Figure 4: Yield (%) of SC-CO_2 antisolvent precipitation of compound A out of isopropanol as a function of mole fraction CO_2, pressure and temperature.

At the end of the synthesis process compound A is recovered as a highly concentrated solution in isopropanol (~ 0.25g/ml). This solution is used without further dilution in the SC-CO_2 antisolvent precipitation process. Figure 4 shows that the efficiency of the precipitation process depends on the mole fraction CO_2 and the temperature. Ninety percent of compound A can be recovered as a powder with a CO_2 mole fraction of 0.77. At 70ºC and 120 bar it is possible to reach a yield of 95 % with a solvent/CO_2 molar ratio of 1/10 or a compound A/CO_2 ratio of 1/280. Increasing the temperature to 80 ºC results in a lower yield. This is probably due to the higher affinity of the compound for isopropanol at higher temperatures.
Similarly, precipitation of compound B out of MEK was performed using CO_2 as antisolvent. Table 1 shows that also this compound can be precipitated with high yields using limited amounts of CO_2.

Table 1: Yield (%) of supercritical fluid precipitation of compound B out of MEK.

Cpd B (g)	CO_2/Cpd B (mole/mole)	CO_2/MEK (mole/mole)	Pressure (Bar)	Temperature (ºC)	Yield (%)
1.377	169.3	19	112	69.9°C	99,1
	159.2	17.9	124.7	70.3°C	98,7
	159.2	17.9	125.0	70.0°C	96,3
1.836	82.4	12.7	119.5	70.6°C	94,5
	88.9	13.7	117.6	70.4°C	99,0
	88.5	13.5	125	70.2°C	98,7

2.754	82.9	9.3	130	71 °C	98,5
	79.3	8.9	125.2	70.6°C	93,4
	83.9	9.4	139.5	70.5°C	97,8

Characterization of the SCF processed material showed that the physicochemical properties of the compounds do not change during SCF processing. Thermal and IR analysis of the SCF treated powders showed that both compounds were crystalline and that no polymorphic changes occurred during precipitation. Moreover, no degradation of the compounds was observed. TGA analysis showed that compound A did not contain any residual solvent after precipitation and "washing" the powder with 5.3 moles CO_2 or a drug/CO_2 molar ratio of 1/2270. Similarly, TGA and GC analysis showed that compound B was dry after SC-CO_2 precipitation and did not contain any significant amounts of residual solvent.

SEM analysis of the compound B before and after precipitation with SC-CO_2 showed that the shape of the crystals did not change but that the particle size was reduced after processing (Figure 5). This may be beneficial for many pharmaceutical formulation processes in which a fine powder is needed to improve dissolution and bioavailability.

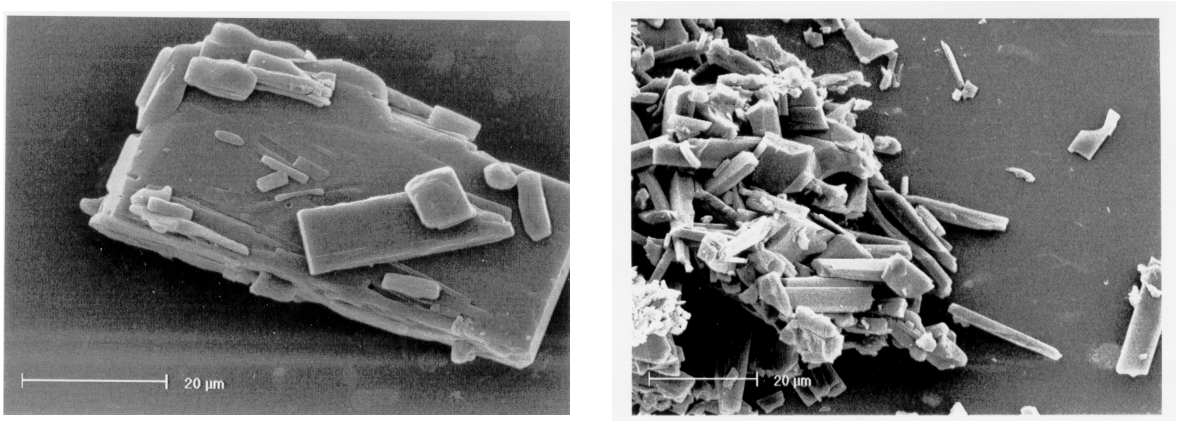


Figure 5: SEM picture of compound B unprocessed (left) or processed (right) with SC-CO_2 antisolvent precipitation process.

Comparison of the costs related to a conventional crystallisation process with the SCF process (Table 2) shows that the conventional process contains many unit operations implying high contamination and operator exposure risks. In addition, cleaning and environmental costs are important for such a process. The SCF process is a fully contained in 1 piece of equipment reducing not only exposure risks but also costs related to maintenance, cleaning etc. As SCF technology is not yet widespread in the pharmaceutical industry, cost of design and manufacture of a production scale unit may be high. A fully contained equipment train for conventional precipitation of potent compounds or parenterals is very costly.

CONCLUSION

The data show that the supercritical antisolvent process can be successfully applied for the crystallization of compounds A and B. The process can be immediately applied to concentrated solutions coming out of the synthesis process. The crystallization occurs with a high yield and does not modify the physicochemical properties of the compounds. Particle size reduction was observed and this may be beneficial for many downstream formulation processes. Comparing the economical impact of the SCF technology with the fully contained

conventional production process shows that the SCF technology is a viable platform technology for the production of highly potent pharmaceuticals.

Table 2: Economic feasibility of SCF process

	Conventional Process	**SCF process**
Investment costs	Final crystallization area plant – 2600 l reactors – Centrifuge dryers – Capacity : 3.5 ton/year 9 processes Small volume area Powder Unit – Sieve – Mill – Homogenizer – Capacity : 10 ton/year 20 processes Note: Both plants need to be fully equipped with isolator technology for potent compounds and parenterals.	One fully contained piece of equipment with isolator technology for recovery of PBOEL 3B compounds and parenterals. Capacity: design related
	Investment Cost ~ 15 M Euros	Investment cost: Dependent on capacity and design.
Operational cost	Manpower Equipment occupancy Throughput time Solvent Use Cleaning Environmental cost Utilities …	Reduced costs compared to conventional process as manpower, solvent use, cleaning costs and environmental costs can be reduced significantly even without recycling CO_2. Estimated cost of CO_2/kg Compound A: 11 Euro

REFERENCES

[1] LIPINSKI C.A., LOMBARDO F., DOMINY B.W., FEENEY P.J., Adv. Drug Deliv. Rev., 23, **1997**, 3

[2] JUNG J., PERRUT M., Journal of Supercritical Fluids 20(3), **2001**, 179.

[3] GILBERT D., PALAKODATY S., YORK P., SCHULTZ T., SHAH D., Proceedings AAPS Annual meeting and exposition, Denver, October 21-25, **2001**, W4528

[4] DE GIOANNIS B., JESTIN P., SUBRA P., Journal of Crystal Growth 262, **2004**, 519

[5] DAINTREE L. S., KORDIKOWSKI A., JIANG Z., GREEN J. A., WILKINS S. A., YORK P. Polymeric Materials Science and Engineering 89, **2003**, 683.

[6] SHEKUNOV B. Y., FEELEY J. C., CHOW A. H. L., TONG H. H. Y., YORK P., Kona 20, **2002**, 178

[7] VANDANA V.,TEJA A., Journal of Chemical and Engineering Data 40 (2), **1995**, 459