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► To cite this version:

S. Papet, Florence Marciacq, Hubert Lochard, Martial Sauceau, Christophe Jousot Dubien, et al.. Supercritical CO₂ antisolvent process for drugs precipitation : from lab-scale to cGMP compliant pilot-scale. 6th International symposium on supercritical fluids, Apr 2003, Versailles, France. pp.1689-1694. hal-01781685

HAL Id: hal-01781685

<https://hal.science/hal-01781685v1>

Submitted on 7 Nov 2018

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SUPERCRITICAL CO₂ ANTISOLVENT PROCESS FOR DRUGS PRECIPITATION: FROM LAB-SCALE TO cGMP COMPLIANT PILOT-SCALE

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INTRODUCTION

Supercritical CO₂ processes have been opening up major horizons for the pharmaceutical, cosmetic and nutraceutical industries. Indeed, regarding the pharmaceutical field, these processes can improve significantly the dissolution rates and therefore the bio-availability of drugs that exhibit very slight solubility in aqueous media and consequently in the human fluids. In this domain, each year, a large number of works are issued and patents filled from worldwide research teams. However, a future industrial development of these techniques requires preliminary steps. Although annual commercial needs of a large number of potential drugs is relatively low (less than 100 tons), it is first necessary to operate a pilot-plant (production up to 5 tons a year) to validate the process before erecting a plant for a larger production. More, the production of drugs in quantity suitable with clinical studies on animals or human beings, in respect with the cGMP rules (current Good Manufacturing Practices) edited by the American FDA (Food and Drug Administration) is also a major need.

In this work, we will describe the scaling-up of a process developed in narrow collaboration with Laboratoires Pierre Fabre and the Ecole des Mines d'Albi-Carmaux. This process concerns the precipitation of an active pharmaceutical ingredient (API) issued from Laboratoires Pierre Fabre research in combination with an excipient. The API exhibits a very low solubility in carbon dioxide and consequently was selected a SAS process with carbon dioxide as anti-solvent and dimethylsulfoxide as solvent. It is based on the enchainment of three different stages: a SAS process, with supercritical carbon dioxide as anti-solvent, followed by a batch step and a final step which consists in a stripping of the residual organic solvent in the powder. We will describe the versatile cGMP pilot-scale apparatus we built specifically in our lab for these applications. We will also briefly give the main impositions related to a cGMP compliance of a supercritical apparatus. Lastly, the characteristics of the product obtained will be compared to those produced on the lab-scale apparatus where the process was first developed.

PILOT-SCALE APPARATUS DESCRIPTION

The pilot-scale has been designed in our lab with the main objective to satisfy to three major key points:

- ✓ The conception and the exploitation have to be cGMP compliant (CQ, IQ, OQ and PQ phases) in its Q7a version (November 2000),
- ✓ The apparatus has to be as versatile as possible, to allow to perform either RESS or SAS and their derivatives,
- ✓ The quantity of powder produced in each batch must be in concordance with the need of clinical studies (few kilograms batches).

The production capacity of the pilot-scale apparatus was determined in order to respect a reasonable scaling-up factor with the lab-scale apparatus (Separex, France) operated in the Ecole des Mines d'Albi-Carmaux (EMAC). Our goal was to lead to a production of round one ton of API a year.

In the table below are presented the major characteristics of the two apparatus:

Criteria	EMAC	CEA
Pressure / Temperature	300 bar / 150 °C	300 bar / 120 °C
CO ₂ max. flow rate (kg.h ⁻¹)	20	500
Solvent max flow rate (kg.h ⁻¹) – way 1	0.6	0-20
Solvent max flow rate (kg.h ⁻¹) – way 2	none	10-100
Autoclaves capacity	2 liters	10 and 50 liters

Table 1: Comparison of the main characteristics of the lab-scale (EMAC) and pilot-scale apparatus (CEA)

Carbon dioxide (Messer France) is cooled, liquefied and stored in a 100 liters vessel (Cefilac, France) maintained at 5°C. The CO₂ circulation is performed using a high pressure membrane pump (Dosapro MiltonRoy, USA) which allows a maximum flow rate up to 500 kg.h⁻¹. The pumped CO₂ is then heated to operating temperature through a heat exchanger. The injection of the different solutions (organic solutions of API and/or excipient) can be operated using two different high pressure membrane pumps (Dosapro MiltonRoy, USA) which cover a flow rate ranging from 0 to 20 kg.h⁻¹ and 10 to 100 kg.h⁻¹. The organic solutions are injected in the precipitation unit either directly or through a nozzle. Three PID controlled flow-meters (Fischer-Rosemount, USA) acting on pumps frequency are used to adjust the CO₂/organic solutions ratio during the precipitation step. The extraction and precipitation vessels were designed and built by Autoclave France in respect with our specifications, the operating parameters can reach 300 bar and 120 °C. Their internal volume is 10 and 50 liters. They can be used either as extraction or precipitation vessels, depending on the process performed and the product treated. The obtained products are retained in the vessels using 5µm removal filters. The solvent/CO₂ separation step is operated using three cyclonic autoclaves

(Autoclave France). Before recycling, the CO₂ is purified through an activated carbon filter. The pilot-scale apparatus is equipped with a large number of sensors (pressure, temperature, flow-rate...) and in particular for the most important operating parameters of the process, in terms of safety and quality management.

Safety related to high pressure is guaranteed by a three stages protection : oversized constructing parameters, overpressure protection by a computer acting on automatic valves and finally by implantation of rupture discs and safety valves.

A schematic diagram of the pilot-scale apparatus is given below (figure 1).

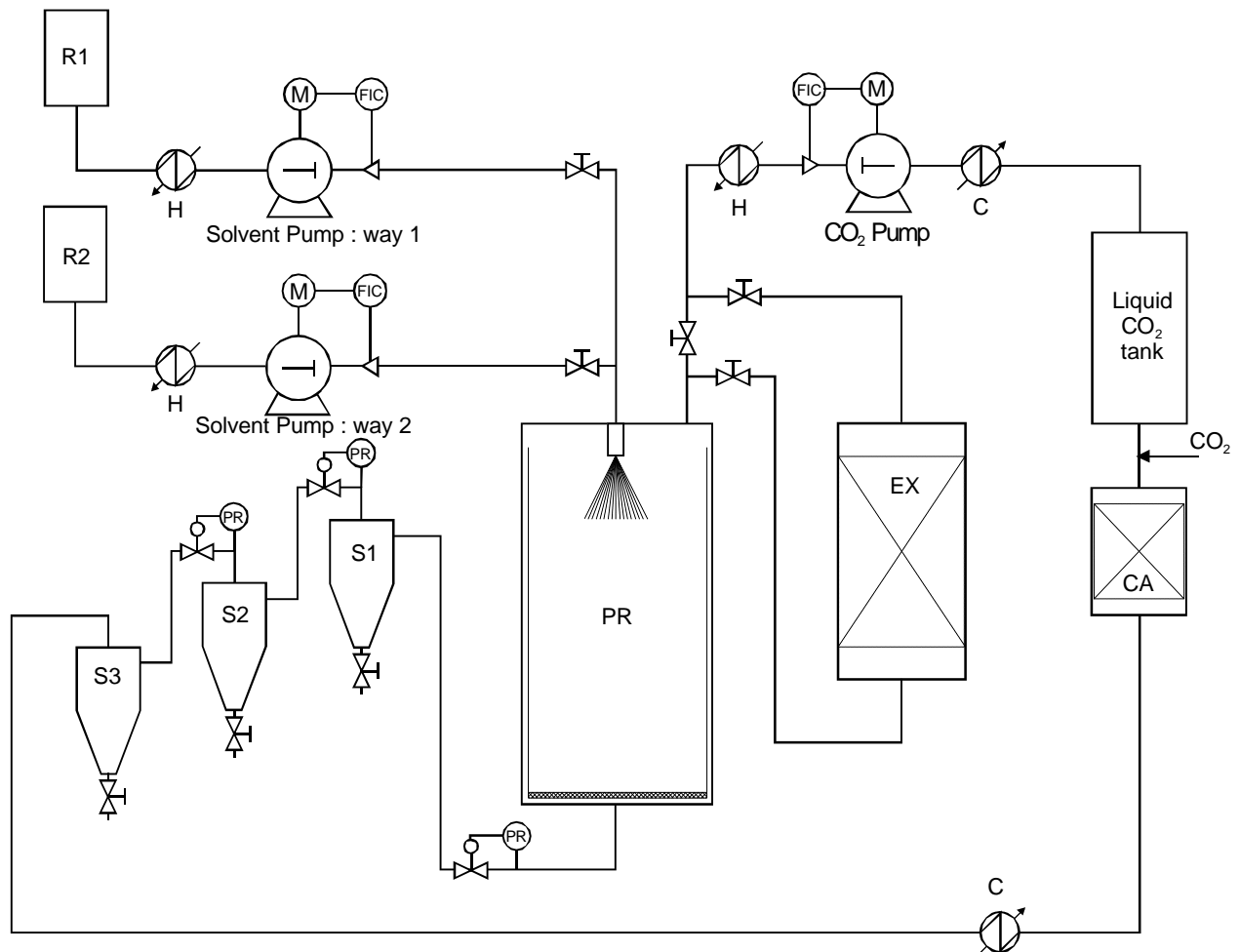


Figure 1: Schematic diagram of the pilot-scale apparatus. (H): Heater, (C): Cooler, (PR): precipitation vessel, (EX): Extraction vessel, (CA): Activated carbon filter, (S1 to S3): Cyclonic separators, (R1 and R2): Solvent tanks.

To respect the cGMP rules, we had to take into account in the early beginning of the conception of the apparatus the separation of all fluxes, either materials fluxes (inlet and outlet products) or staff fluxes. The pilot-scale apparatus is consequently located in different parts of the building where safety (for the staff and the API) was evaluated individually.

A dedicated zone was attributed to the handling of the API (inlet and outlet) with a specific air treatment and a high cleaning efficiency.

To insure a cGMP compliance, the apparatus cleaning process has to be very efficient either in a single or multiple product operating case. This aspect, certainly the major one, has also been integrated in the early stage of the conception. All equipments have been conceived to minimize contamination between two consecutive batches.

All the vessels constituting the apparatus were designed to promote their cleaning efficiency, whether cleaning is manual or automatic. Their internal design is then oriented to ban or reduce as much as possible all the parts where powder could accumulate and could be consequently difficult to remove. Sensors (pressure, flow-meter and so on) were chosen in respect with the same criteria.

A view of a part of the apparatus is given in the figure 2.



Figure 2: View of the apparatus (extraction vessel)

Due to high pressure technology and for a maximum reproducibility of cleaning step, we have chosen to develop an automatic way using supercritical carbon dioxide circulation alone or mixed with an organic solvent. Indeed a manual route of cleaning, operated by the staff, can not be guaranteed as reproducible as an automatic way is. However, some parts of the apparatus can not be cleaned automatically and must be manually cleaned and/or dedicated to a single product. For example, this is the case for the porous filter retaining the powder in the precipitation unit.

The validation of the cleaning is actually under progress. Beside determining the best operating conditions, in terms of flow rate, pressure or so on, it is necessary to identify clearly where sampling is important to control the efficiency of the cleaning process and also insure a perfect status of the equipment. Those locations must be as numerous as necessary to validate this step. They are chosen at “critical” points of the pilot-scale apparatus, that is to say locations where powder could accumulate and could be hardly removed by the CO₂ and/or solvent fluxes.

RESULTS OBTAINED

As mentioned previously, we have chosen to evaluate the performances of this apparatus with a process developed elsewhere [1]. This SAS process is based on three steps:

1. The API is precipitated with cyclodextrin (Wacker Cavamax W8 Pharma) using dimethylsulfoxide (Atofina France, purity > 99.98%) as solvent and CO₂ (Messer France, purity > 99.7%) as anti-solvent. The CO₂/solvent ratio is commonly in the range 50-200, the pressure in the precipitation vessel is round 250 bar and the temperature is round 40 °C.
2. The product is maintained under a CO₂ pressure for many hours to promote inclusion of the API in the cyclodextrins.
3. Lastly, the product is washed with carbon dioxide to remove all the solvent residues to respect the rules on solvent residual quantity in pharmaceutical products.

The influence of operating parameters on the characteristics of the powder during each steps is described elsewhere [1]. The API concentration in the final powder was measured using HPLC (Merck KGaA, Germany), and the residual solvent content was measured by GPC (Agilent, USA). We chose the dissolution rate as criteria to compare the results obtained on the pilot-scale and on the lab-scale apparatus. The dissolution rate was measured *in vitro* at 37°C. The equivalent of 100 mg of API is introduced in 100 ml of an aqueous solution containing sodium-dodecyl-sulfate (SDS France, 5% m/v). Periodically, 2 ml of solution were sampled and the concentration of dissolved active compound was measured by HPLC. Dissolution rate of the pure pharmaceutical compound in the same conditions is round 6µg/ml at 5 min. Dissolution rate results are presented in the figure 3.

The obtained production is round a few kilograms in each batch. Approximately ten batches were produced involving this process, no major variations were observed between the lab and the pilot-scale equipments, in terms of yield and powder characterizations. The obtained powder is easily handled, the yield is commonly round 85% (relatively to the API). The process we developed seems to be rather reproducible. The scaling-up factor between the two apparatus (CEA and EMAC) is round 20 in this case. Although this factor is relatively high, the results obtained are comparable. As presented in the figure 3, the dissolutions rates are similar. More, the API content in the final powder is round 10% in the two cases. The residual dimethylsulfoxide content is round 4000 ppm, which is in concordance with the rules edited by the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use.

These results reveal that scaling-up such a process seems relatively easy and leads to consider possible a rapid industrial development of this technology. Nevertheless, more characterization of the powder will be necessary to confirm this first observation, such as DSC measurements or API stability study.

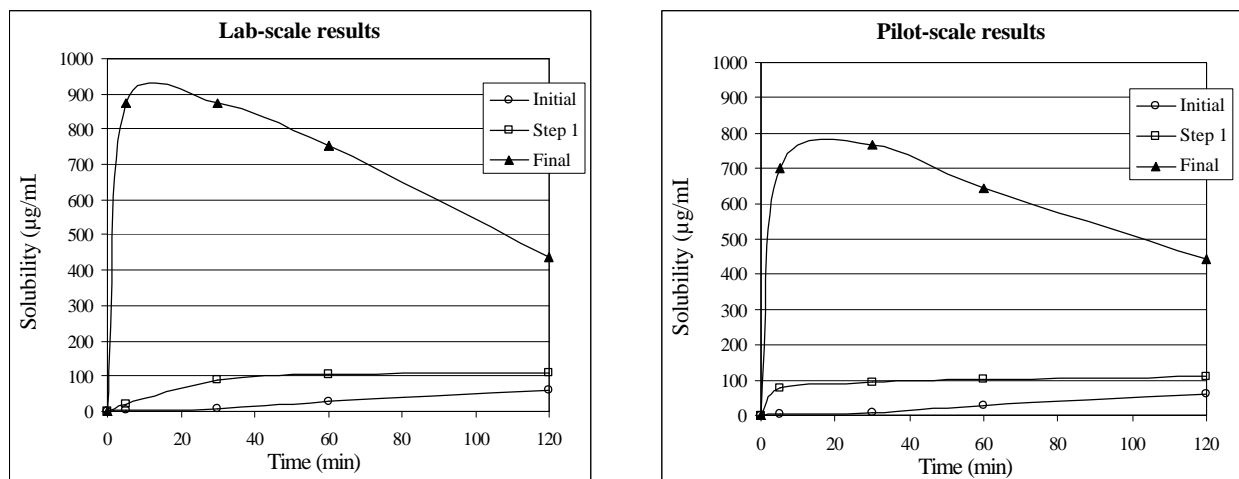


Figure 3: Dissolution rates comparison of powder obtained on lab-scale and pilot-scale apparatus. Data are given before supercritical treatment (initial), after the first step of the process (step 1) and after the full treatment (final).

CONCLUSION

Our goal was to build a pilot-scale apparatus dedicated to the production of significant batches of pharmaceutical compound involving supercritical processes, such as SAS process, RESS process and their derivatives. This pilot-scale has been built and qualified under cGMP rules. The apparatus, depending on the case of study, is suitable to produce up to one ton of active compound a year.

The first results concerning a SAS process performed on an API precipitated with cyclodextrins show that the scaling-up seems to be relatively easy from lab-scale to pilot-scale and that the main characteristics of the final powder are well-preserved. The next steps of our work concern the achievement of cleaning validation, production of batches for clinical studies and data acquisition for a future industrial development of the technology.

REFERENCES

- [1] Lochard H. et al. "A new supercritical process to improve the dissolution rate of pharmaceutical compound", 6th International Symposium on Supercritical Fluids, Versailles, France.