EQUIPMENT FOR SCF PROCESSING OF HAZARDOUS BIOLOGICALLY-ACTIVE POWDERS

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INTRODUCTION :

SCF processing of pharmaceutical products is an attractive field where many research teams are now investing a lot of efforts. Next to the necessary fundamental understanding and optimisation of SCF processes, and to the continuous improvement of GMP practices to allow pharmaceutical processing in these complex installations, the safety issues relating to the handling of potentially very toxic molecules under high pressure remains a permanent concern for the operators.

Very few papers are dealing with safety considerations in supercritical fluid processes [1]. For instance, despite the new regulatory requirements on the design of safety systems, very few is known and published on the design of safety valves operating with supercritical CO_2 [2]. The same conclusions can be drawn for the manipulation of toxic substances in these high pressure systems. Even if most people work with “model” non-toxic compounds at lab scale, it is now necessary to prove the feasibility of the technology on pharmaceutical chemical entities of interest both at lab and production scale. This requires special equipment and need to be considered both during equipment design and process operation.

This paper will present the main issues relating to the processing of these compounds and will propose different solutions used for operating at lab and production scale with toxic products.

MAIN HAZARDS RELATED TO THE PROCESSING OF HAZARDOUS BIOLOGICALLY ACTIVE POWDERS:

First of all, the usual hazards already present in traditional processes where we find fine active powders still remain. Explosion hazards due to the handling of fine powders, biological activity of the compounds and the related consequences for the operator protection and for the equipment cleaning are of course to be considered with the greatest care. For these hazards we will refer to the main equipment standards dealing with explosion proof equipment standard [3] and clean room and environment concept [4].

But some of these usual hazards are dramatically emphasized by handling in compressed fluids and the related risks of leaks, quick decompression, and possible formation of aerosols in the working area.
The prevention of environment contamination by very fine powder release and the operator protection in the working area in the case of leaks or aerosol projection are therefore the two major areas of concern that will have consequences both on equipment design and operation.

Clean equipment design, process and equipment validation, and prevention of cross contamination are also permanent concerns of any pharmaceutical process. It seems to be a

more critical issue here on SCF equipment for many reasons. First of all, the complexity of the process and of the equipment that are composed of many small high pressure parts, sometimes difficult to clean, is a first difficulty. But these processes also integrate complex fluid recycle loop that is are major source of contamination. Cross contamination and contamination by external pollutants in the equipment will therefore be carefully checked and optimised.

This will require special procedures for the equipment design of the safety systems and for the operation of these systems.

EQUIPMENT DESIGN ASPECTS :

Contamination issues

The first risk of cross contamination comes from fluid recycling. Fluid recycling that is usually not necessary at lab scale becomes mandatory for most SCF processes at large-scale [5]. The usual gravity separator or the improved cyclonic separators cannot have a perfect efficiency. Moreover, we cannot avoid to have traces of very fine particles or organic solvent concentration variation in the recycling fluid. This causes a possible risk of entrainment and product recycling, that has to be minimized to reduce the risk of cross contamination even if is possible to clean the equipment. A very simple method, firstly proposed for the preparative supercritical fluid chromatography [6] permits to maintain a constant co-solvent concentration in the fluid for the anti-solvent process. The system based on the Gibbs' law, consists in scrubbing the CO_2 flow at a constant pressure and temperature. The outlet flow is therefore maintained at constant composition and possible contaminants are trapped in the saturation column.

The second risk comes from the CO_2 supply system. This system must be designed to avoid any contamination. As back flow through check valves is always possible, it is recommended to have a separate On/Off valve that stops CO_2 flow when the feed line is not used and when there is a risk of back flow from the process. Other preventative actions consist in using a dedicated feed line from the bulk storage to the process equipment. It is also necessary to have a full traceabilty of both the bulk CO_2 for GMP compliance but also for the storage itself as some of the cylinders are provided by gas suppliers without any precaution. The possibility to clean storage tanks and eliminate the possibility of contamination coming from or going to the storage is mandatory.

Then, it is recommended to split the equipment in different parts with a maximum protection to avoid contamination. The pumping section could be separated from the separation and crystallisation / atomisation sections by high efficiency filters and independent vent lines. SEPAREX developed for this purpose high pressure ceramic filters with nanometric filtration rate.

At last but not least, the components will all have to be designed to ease cleaning, with high quality electro-polished surfaces, zero dead volumes, and easy cleaning connections for the different fittings, instrumentation, etc. Drains and access points shall be located to permit efficient cleaning procedures that will be carefully designed and checked.

Atmosphere release and venting issues

Due the presence of biologically active compounds under pressure, the sudden release and unavoidable entrainment of compounds from a vessel through a safety valve or during a depressurisation must be considered. A single vent line or a simple atmospheric pressure vessel in which one could expect to precipitate all contaminants, is not sufficient to guarantee that no active powder will be entrained in the atmosphere or in the building air exhaust system.

Different methods are proposed:

- High pressure filters can be placed on most of the drain and depressurisation valves, but these filters cannot be placed on the safety vent line where the flow must be free of obstacles before being released.

- A more efficient method consists in scrubbing the effluents by a liquid. The gas is percolated in a good solvent of the product and leaves the scrubber free of powder. The design of the scrubber must be made carefully to avoid any entrainment of solvent in the vent, in case of sudden high flow rate release. The presence of liquid and the guarantee to have a good solvent of the products must be checked before any operation of the system.

- The only method that guarantees a perfect containment of all the vented products is to design a venting system with a large vent vessel followed by a high efficiency filtration system. The vent vessel will be sufficiently large to be able to contain the whole capacity of the equipment, so that even in case of a simultaneous filter obstruction with a complete depressurisation of the equipment, the complete containment is still guaranteed. In the case of a 10 kg CO_2 capacity system, it consists of a 5000-litre atmospheric pressure vessel or a 500-litre vessel designed at 10 bar! If this is a solution for lab and pilot scale systems, alternative solutions have to be found for the design of larger production scale equipment where the active products will have to be kept as long as possible inside the contained area of the equipment.

OPERATION ASPECTS

Clean and protected environment solutions

Equipment containing toxic products is usually placed in a clean room maintained in depression and equipped with a double air lock system for inlets/outlets.

If this solution protects the equipment environment, it does not eliminate the venting system used to contain the exhaust flows and the body protection for the operator that is necessary in case of leak or in case of contact with the active.
For this reason, and in order to be able to work on the most toxic molecules (cytotoxic, new chemical entities with unknown toxicity, etc.) where we usually have very small quantities of product, we have developed a very small scale equipment placed in an isolator (figure 1). This provides the advantage of having a perfect containment with the possibility to work in

clean and possibly sterile environment, with a single protection, for both the environment and the operator. It reduces the air volume to be treated and is found to be an economical way of working with hazardous products.
The isolator will be preferably manufactured with safety glass or with polycarbonate to have both a good mechanical resistance to projections, and solvent resistance. In case of utilisation of flammable or explosive solvents, solvent sensors shall be put in the isolator. Components will be manufactured with ex-proof standards or the isolator will allow a nitrogen blanketing.

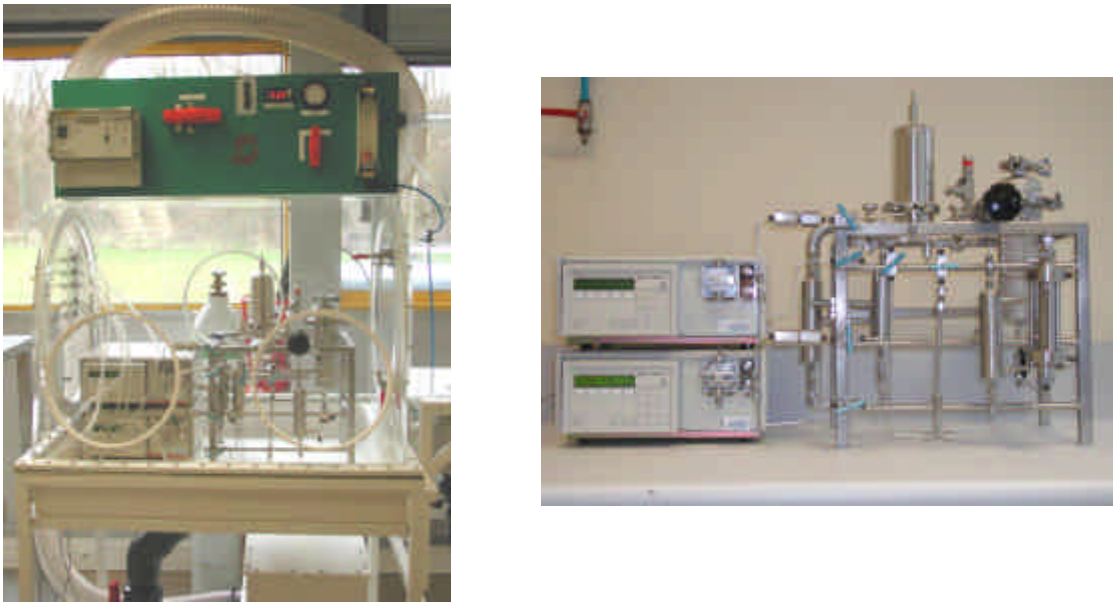

Figure 1 : New chemical entities process screening equipment placed in an isolator

When larger equipment is used, the general arrangement of the process component will have to be carefully studied so that the risk of contamination is reduced. High-level containment devices like isolator or laminar flux will be used for the critical parts of the process, (particle formation or particle collection vessels) as the other parts of the process are in a clean room with lower air quality level. To ease the cleaning and to maintain high air quality, we need to place the minimum amount of components in “ultra clean” environment, but we need to keep all the parts potentially exposed to the active product, protected from any active contamination (figure 2 and 3).

Preventative maintenance, periodic inspection of all seals, valves, pumps, etc… are of course recommended.
Component design will avoid dynamic seals, threaded parts and all fragile dynamic parts more likely to be potential sources of contamination, and rupture.

Body protection and automation solutions

When it is not possible to place the equipment behind an isolator, it becomes mandatory to consider the possible hazards related to the immediate proximity of the operator with high-pressure parts containing CO2 + active hazardous substances. Body protections (masks,

complete body protection, or mask equipped with independent air breathing system) must be imposed according to the chemical and physical properties of the manufactured products.

Emergency procedures that will consider the risk of fire, the risk of very big leaks and large product contamination must be put in place in the lab or in the factory. Quick evacuation plans for the personnel and procedures associated with the risks of environment contamination, maintenance and cleaning procedures to be planned after the accident, must be considered.

Even if ventilation systems of clean rooms are large and usually oversized with quick air renewal rates, the available space is low and a quick CO_2 release in the room can lead to high CO_2 concentrations. CO_2 detectors must be available with special emergency procedures for the personnel.

In any case, automated operation is to be recommended when possible, especially automated depressurisation procedures that have to be carefully optimised and controlled in order to avoid line plugging with powder or with dry ice, but also to avoid contamination of equipment parts.
Automated high-pressure vessel opening/closing systems will have to be put in place for large vessels. The cleanness and non contamination of these automated systems (seals, lubricants, actuators, etc.) have to be appreciated.

Figure 2: "Ultra clean" 7-litre pilot scale equipment designed in 2 skids to be placed in a "grey" room (pumping, heating, vent) and in class B environment for the main particle formation vessel.

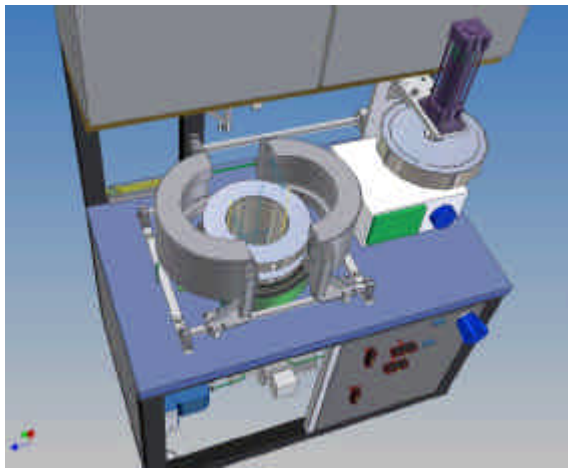

Figure 3: Drawing of the automated opening closing system.

For large production vessels, fully automated systems operating under large laminar flow hoods are recommended, not only for safety, but also for cleaning and economical considerations.

Finally, any process concept allowing to combine the powder formation process and the prior or further manufacturing steps (purification, drying, formulation, packaging, etc.) will of

course reduce the risk associated with the handling of these hazardous process and probably reduce the manufacturing cost.

CONCLUSION

Keeping the best possible level of safety on SCF processes is crucial for the development of this new technology; and any accident would have a dramatic impact on the future of many pharmaceutical applications actually under development.
A systemic approach where safety considerations takes into account the high-pressure process engineering, particle engineering, clean rooms concepts, biology, formulation and galenic approaches, is the key for the success of these new process developments.

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