SCF Particle generation in compliance with GMP

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Abstract:

Generation of various types of particles (nano-, micro-, neat or composite particles) for pharmaceutical applications is focusing significant R&D efforts worldwide. However, most works are completed on small-scale equipment, leading to attractive results that only demonstrate the process feasibility without any evaluation of scale-up issues.

At the difference with most other industrial fields, manufacture of medicinal products is strictly submitted to drastic rules, defined by regulatory authorities, that can be gathered in a corpus called cGMP (current Good Manufacture Practice). Entering a new technology like SCF particle design is raising significant difficulties to convince the authority auditors of compliance with GMP. This implies a complete "revisit" of the process design and the integration of the basic concepts into a whole installation constructed and operated according to these stringent standards. At a moment when the situation is moving and the "pipe-line" is now rich of several formulations to be shortly introduced for pre-clinical or clinical trials, especially for manufacturing inhalable particles, enhanced bio-availability formulations, and stabilized bio-molecule composites, we briefly present how we are trying to improve the acceptance of SCF particle generation through the design and operation of SCF equipment installed in a compliant environment (clean room, effluent control, operator protection, etc.). We would conclude that, based on our growing experience in the field, clinical lots preparation and scale-up in compliance with GMP are accessible at present, and that several issues, which were regarded as bottlenecks, have been successfully addressed, making it possible to envisage a near commercial manufacture.

Introduction

Supercritical Fluid technology is not yet widespread in the pharmaceutical industry, except for extraction of active compounds from vegetal sources (phytopharma-/nutraceuticals) and preparative chromatography. However, many innovative drug formulations based on SCF technology are now under development, demanding a wide R&D effort as process choice and optimization shall be adapted case-by-case on technical and economic basis. Particle formation processes using supercritical fluids [1-3] are now subjected to an acute interest, especially for increasing bio-availability, designing sustained-release formulations and developing non-invasive routes of administration. Moreover, the intrinsic sterility of SCF processes [4] will appear as a major advantage for preferring these environment-friendly solutions, working in low-temperature conditions.

In fact, SCF technology comprises several processes to prepare various forms or formulations of the drug (dry inhalable powder, nano-particle suspension, micro-spheres or micro-capsules of drug embedded in a carrier, drug-impregnated excipient or matrix,…). Moreover, although most previous works dealt with water-insoluble (or poorly soluble) molecules, recent

development permits to also process very hydrophilic molecules, including fragile bio-molecules.

Most of these promising works have been completed at a small-scale. Nevertheless, a convincing evaluation of the biopharmaceutical performance of these new formulations, even at the earliest stages of development (proof of concept in animals, stability, tolerance), requires the ability to produce a sufficient amount of particles in a reproducible way (batch to batch consistency). It is therefore not surprising that very few published works have assessed the "pharmaceutical" performance of such SCF processed particles, slowing down the spreading of these promising processes in the pharmaceutical industry. Thus, the major difficulties slowing the commercial development are related to process scale-up and operation in compliance with GMP that require not only a usual scale-up but a complete re-examination of all the equipment and operation procedures [5].

It is definitely not possible to scale-up on a pure process point-of-view what is known and applicable at lab or pilot-scale and, according to our experience, everything must be "revisited", especially "side-aspects" that are generally neglected on non-GMP equipment. We will try to give some examples of how we are trying to progress towards GMP acceptance of SCF particle design and formulation.

Bio-availability enhancement for poorly-soluble drugs

It has been shown that, for many poorly-soluble compounds orally administered, the bio-absorption process is rate-limited by the dissolution in gastro-intestinal fluids. Particle size reduction *theoretically* leads to dissolution enhancement by increasing the surface area between the drug and the dissolution medium. Nevertheless, in many cases, cohesive forces between the micronised particles are limiting the accessibility of the dissolution surface and this results in an unpredictable effect on dissolution rate [6]. Moreover, collecting and handling *"flying"* nano-/micro-particles are very difficult in a reliable and safe way, and complicate the downstream processing (tabletting,...).

In order to match the need for increased specific surface area while complying to GMP, we had to propose an innovative approach : the micronised particles generated during RESS or ASES process are collected by deep-bed filtration on a water-soluble excipient bed [7,8]. Micronised particles are "stuck" on the surface of the carrier, probably by Van-der-Walls forces (figure 1). Surprisingly, very few particles remain untrapped and the material can be handled without dust emission as a free-flowing powder, readily processable and offering a good access to particle surface for dissolution.

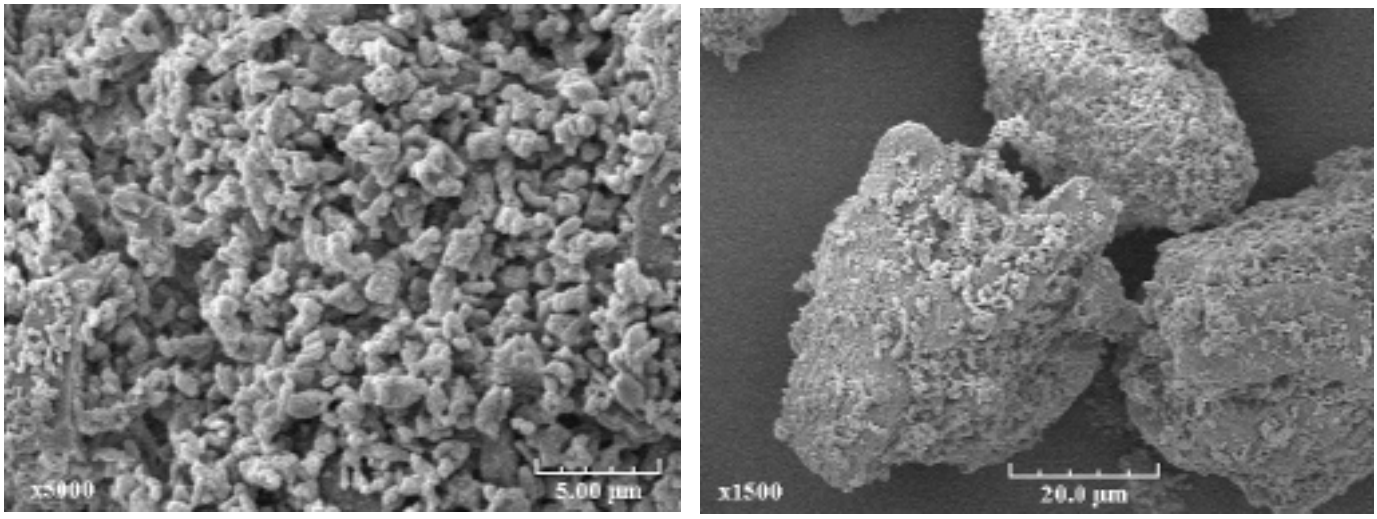

Figure 1
Lovastatin micro-particles trapped on lactose granules

Inhalable particles

Widely used for the treatment of respiratory diseases, the direct delivery of drugs to the lung receives more and more attention for systemic delivery, including bio-molecules. Applications of pulmonary delivery have recently emerged either as an alternative to injection for drugs that have a poor absorption by other non-invasive routes, increasing patient compliance and minimizing side-effects, or for situations where a more rapid absorption of drugs than it can be achieved by other non-invasive routes is required. Aerosol delivery of therapeutic drugs requires a narrow particle size distribution (1-5 µm) without re-agglomeration and morphology or structure modifications during both processing and storage. Supercritical fluid processes appear as good candidates for manufacturing such particles, for both "small" molecules and bio-molecules [9].

GMP-compliant equipment design, construction and operation

We already built several pilot-scale or semi-industrial particle-design plants under strict quality assurance and documentation. Much attention must be paid to operation, maintenance and cleaning procedures since the very beginning of the equipment construction. The technical choice of any part must be considered in order to match GMP requirements (tubing and autoclave polishing, valve lubrication, dust deposition, etc.) with a special attention to cleaning that must be carefully organized with many consequences on hardware design. Instrumentation and data logging are also compliant, so as all environmental parameters inside the clean room where the installation is installed.

The semi-industrial supercritical fluid particle design equipment shown on figure 2 was recently designed and built: We completely reconsidered the process itself (RESS or ASES) and developed innovative solutions, more precisely for particle collection (selection of new filter media, design of the bag-filter and atomisation vessel), fluid recycle and waste management as no effluent containing API could be rejected outside.

Figure 2
GMP-compliant equipment for manufacture of clinical lots of inhalable particles.

Safety and environment management

Manufacture and handling of very fine powders of nano-/micro-particles must be subjected to a very careful safety analysis, especially when high-potent APIs are concerned. Protection of the operators is a key-issue (figure 4), while protection of the API from any contamination is also a key-issue referring to GMP. And it is not so simple to combine these two constraints that may be contradictory, especially when choosing the pressure map inside a clean room receiving a high-pressure equipment, and its access rooms (figure 3). The main non-accidental hazard is related to particle release at the end of the run when the powder must be recovered. This issue is addressed by a careful design of the equipment, particularly of the atomisation vessel from where the atomised powder collected onto a bag-filter shall be extracted without

external release; moreover, the transfer of the particles from this bag to a safe container shall be operated inside a laminar-flow hood with complete filtration of the effluent air.

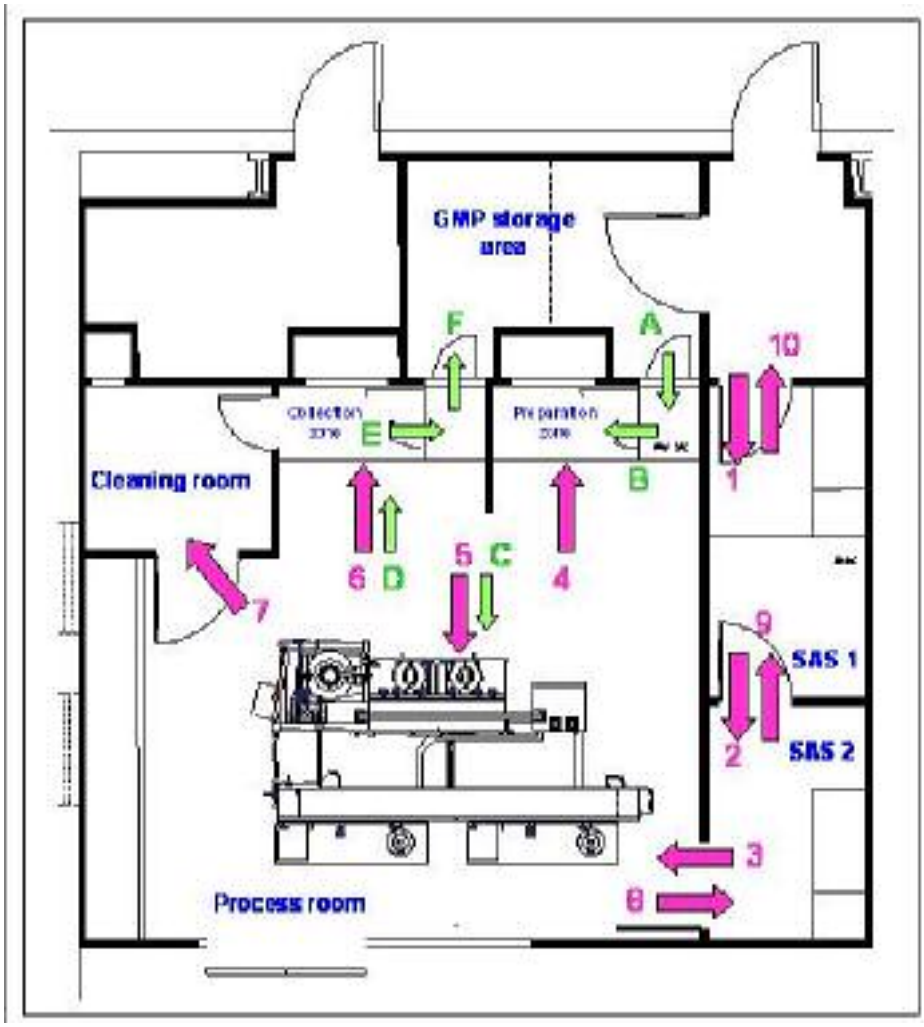

Figure 3 :
SEPAREX clean room for GMP manufacturing of high-potent APIs
(green arrows : API, pink arrows : operators).

Environmental issues must also be considered before design and operation. No need to say that any emission of fine API particles carried by gaseous effluents or an accidental release from a SCF equipment is not acceptable ! This requires a complete filtration of the air exiting from the clean room and of any gaseous effluent released to atmosphere, demanding a safe and redundant filter system on the vent lines. This system must be designed in order to avoid any plugging of these lines considered as the basic safety tools in any supercritical equipment (collection of effluents from rupture disks, safety relief valves and depressurisation/purge valves). Never forget the risk of formation of dry ice in vent lines and filters downward purge valves ! In extreme cases, especially when the fluid is not carbon dioxide, another constraint may be to collect the gaseous effluents – potentially carrying substantial amounts of API - for further waste management (e.g. incineration), complicating the combination of equipment safety and environment protection.

Figure 4
Operating a GMP-compliant equipment for manufacture of particles of a high-potent API in compliance with GMP.

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