

NEW TECHNOLOGIES FOR SAFE AND CONTAINED POWDER HANDLING IN THE BULK PHARMACEUTICAL INDUSTRY

Solutions to complex powder handling issues when
designing a new factory for bulk pharmaceuticals

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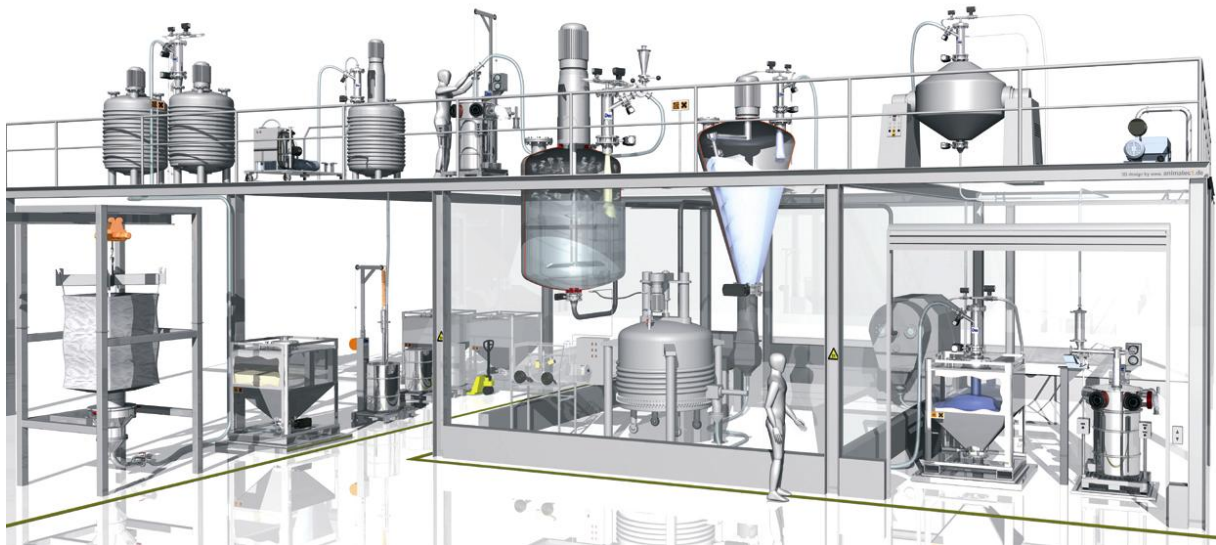


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1. Introduction

The pharmaceutical industry is facing important changes due to the evolution of the market in the last decade (expiration of patents and increasing strength of generic companies, pressure from national government to decrease the price of medicine, increasing costs for developing new medication and shorter life cycle of the product, etc.).

Pharmaceutical companies are forced to review their way of production in order to become more competitive and at the same time are obliged to respect ever more stringent production guidelines.

In order to improve their productivity, existing and new manufacturing facilities need to be modified and designed in a more flexible way in order to adapt quickly to the constant changes of the market, the safety and the quality control standards etc. The operation and maintenance costs must be kept to a minimum.

Powder handling plays a major role in the design and the operation of an API facility, and can often become the “bottle neck” of the plant.

Previously, manually loading powder through a manhole was in most cases the preferred method for charging process equipments. Therefore, problems related to containment, safety and logistics were part of everyday life for the persons in charge of production.

The constantly increasing toxicity and reactivity of products in recent years as well as the ever more demanding production standards with regard to quality have made closed powder handling an unavoidable factor and manual handling obsolete.

Selecting a suitable technology has become vital for the development of a project since it can largely influence the entire design of the installation, from the civil engineering to the dimensioning of the process equipment, and, as a result, greatly effect investment costs and, subsequently, operating costs.

2. Plant design

The issue of powder handling has always been present at the various stages of producing chemical and pharmaceutical products. In the past, however, it was often neglected and considered at a later stage when working out the details of the design of production units.

Manually loading powder through an open manhole was usually the method selected for charging a vessel.

Such open handling poses various problems in terms of risk of cross contamination, safety and poor ergonomics.

Furthermore, the lack of planning at the beginning of a project gives the following problems when later deciding to upgrade the production unit in order to improve hygiene and safety during powder handling:



Powder charging through an open manhole

- The lack of space greatly limited the choice of technology or the possibility to partition the installation.
- The logistics of the raw materials were limited by the layout of the equipment.

Nowadays, a pharmaceutical facility should be designed for multipurpose operations in order to adapt quickly to the market requirements. The design of the production unit should allow fast changes of the process by using mobile and modular technologies.

The powder handling technologies should be able, if possible, to handle different types of packaging (drum, bag, Big-Bag, etc.) and at the same time should allow the transfer of small and large quantities of powder.

A multipurpose plant should be designed with a certain degree of upgradeability in order to be able to adapt quickly to the frequent change of processes. Different levels of containment are usually required in a production facility depending on the process step and the characteristics of the products (toxicity, MIE, etc.).

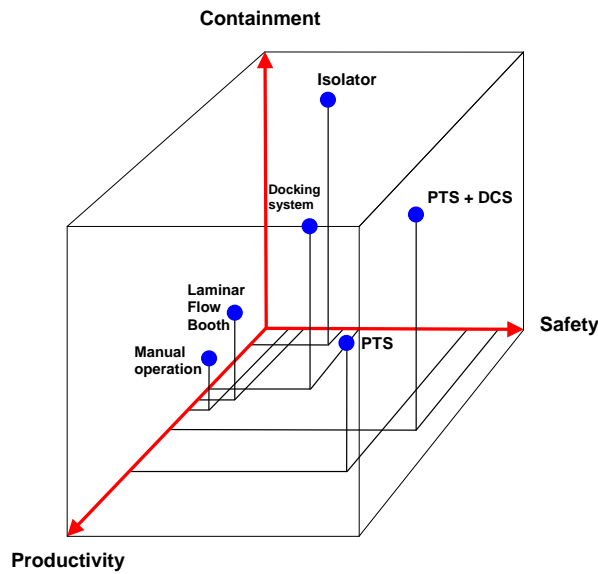
The powder handling technologies should be designed in order to handle powders with various levels of containment.

In the past, productivity was not the main concern of the pharmaceutical industry. However, due to the new challenges pose to the industry, pharmaceutical companies are forced to review their way of production in order to be more competitive.

In order to improve their productivity, existing and new manufacturing facilities need to be modified and designed in a more flexible way in order to adapt quickly to the constant changes of the market, the safety and the quality control standards etc. The cost of operation and maintenance must be monitored permanently and kept at a minimum.

In order to determine the most appropriate equipment when designing a new production unit, the following parameters must be analyzed:

- Amount and type of powder to be handled
- Type of packaging (drums, etc.)
- Product coming from an internal production site or an external source
- Characteristics of products (toxicity, explosiveness, reaction to moisture, etc.)
- Need for intermediate storage (quarantine)
- Type of equipment to be charged and type of process (presence of solvents)
- Level of containment (sterile unit)
- Duration of the batches in relation to the equipment



Relation of containment, productivity and safety

Over the last years, a fresh approach to designing new pharmaceutical production units has emerged which aims at decreasing manual handling and increasing the containment of the powders.

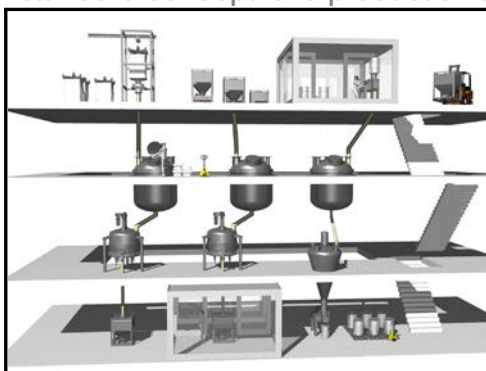
The constantly increasing toxicity and reactivity of products in recent years as well as the rising production standards with regard to quality have made containment an unavoidable factor.

Containment is as important for the protection of the operators as it is for the product itself to prevent any external contamination.

In order to improve the method of openly charging a vessel through the manhole, several approaches have been applied. They mainly use the concept of loading powder by gravity, but with improved loading devices.

Such methods were able to improve the hygiene of the operation according the cGMP standard and the protection of the operator, however often at the costs of the performance of the plant and without solving the inherent problem of safety).

2.1 Standard concept for a production unit: Loading by gravity



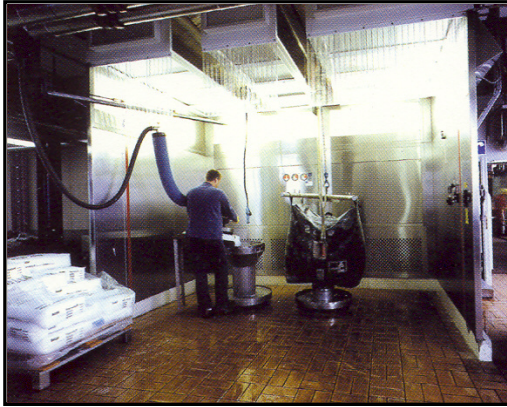
Loading by gravity

The choice between the various approaches is based on the toxicity of the powders, the amount to be charged and the type of packaging. Often different approaches coexist within the same production unit.

Most frequently, the powder is located on a higher floor and falls through a chute into production equipment (dryer, reactor, etc) located on a lower floor.



The loading zone can be confined, e.g. by a laminar flow booth, and the drums can be emptied with a drum lifting system. In this particular case, it is necessary to protect the operators with safety suits and gas masks with external breathing air. However, the safety of the operators is still not fully guaranteed and furthermore, the protective gear makes working difficult.



Laminar Flow Booth

The problem of dust formation inside the booth has not yet been solved. This frequently causes clogged filters, long cleaning times, and high maintenance costs for the replacement of the filters.

Another common approach uses containers equipped with special automatic connecting valves (active and passive), allowing the container to be connected and disconnected in an almost air-tight manner.

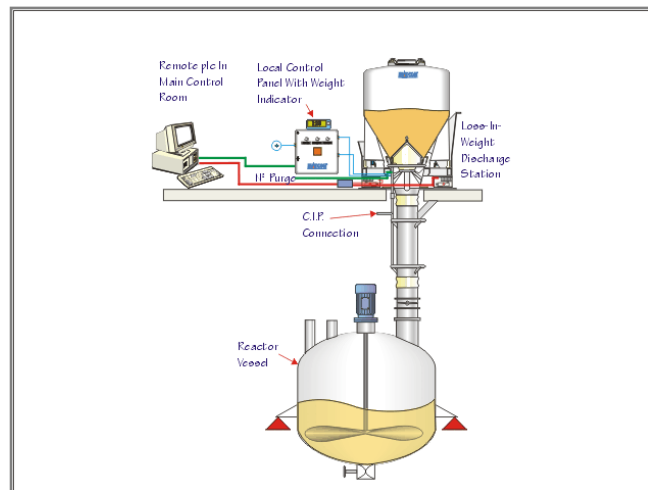
This solution makes it possible to deal with large quantities of powder (> 100 kg) while decreasing the need for manual handling. It is also useful when dealing with an intermediate product that needs to be stored or quarantined between stages of

production.

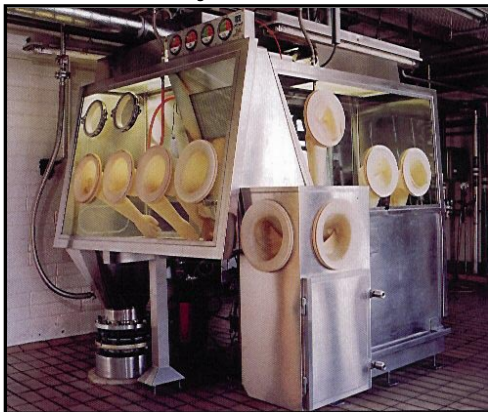
Although appealing at a conceptual level, this solution shows its limitations quickly when it is applied on a large scale in a new production unit.

Not only the investment in a park of containers, but also the need to set up expensive cleaning equipment as well as maintenance of complex mechanical parts make this solution expensive.

This system is not flexible when it comes to charging small amounts of powder or when the powder is delivered in various types of packaging (bags, drums, etc.). It is also rather limited as soon as the product is very toxic ($50\mu\text{g}/\text{m}^3$), explosive or when it has poor flow characteristics.



One of the only solutions when dealing with very toxic products is the use of a glove box. It provides good protection for the operator, the product and the environment. However, since they are designed for specific tasks, glove boxes offer very little flexibility. They take up a lot of space and the investment costs are substantial.



Glove Box

Considering these various solutions, powder is loaded by gravity into various types of vessels. Due to the space required by these installations, it is usually necessary to provide a separate room on the upper floor just for the powder handling.

The connecting tube between the loading zone and the equipment to be charged is often a source of problems. The well-known phenomenon of clogged-chutes occurs frequently when handling products

with poor flow characteristics or when there is a lot of moisture present during loading. Neither cleaning nor validations of these tubes, which are often several meters long, are easy.

Finally, the layout of the equipment is dictated by the flow characteristics of the powder and not necessarily by any logical process order. Such concepts lead to design expensive production plants with several floors, which offer little flexibility for subsequent modifications of the production equipment.

Furthermore, these different approaches are primarily based on the need to improve the containment of powders, without taking into consideration for instance the safety issues concerning the risks of explosion.

2.2 Containment

The increased reactivity and toxicity of products in conjunction with ever more stringent production guidelines lead the industry to implement closed powder handling at every step of the plant.

In production units it has become standard practice to guarantee a containment level of less than 1 microgram/m³. Open powder handling is no longer possible and the choice of a containment method is inescapable in order to guarantee the security of both operators and product.

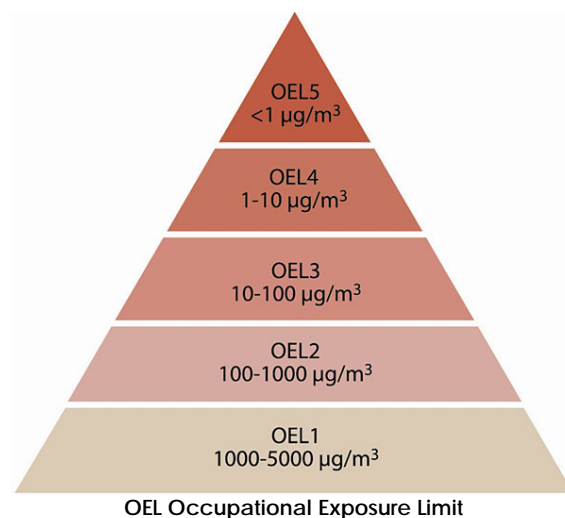
OEB/OEL 5 : Highly toxic

OEB/OEL 4 : Toxic

OEB/OEL 3 : Less toxic

OEB/OEL 2 : Almost non-toxic

OEB/OEL 1 : Non - toxic



It is still common practice to protect operators by wearing full safety suits with gas masks or external breathing air. Industries try to move away from such practices as the safety of the operator is not fully guaranteed and work under these conditions is rather difficult and unpleasant. For instance, the COSHH regulation (Control of Substances Hazardous to Health, UK) clearly indicate that personal protective equipment should be used only as a last resort and never as a replacement for other control measures which are required (engineering controls).

Furthermore, the protection of the product and the environment is still not assured therefore a fully enclosed special production area with complex ventilation and filtration systems is required.

The trend in the development and production of new API's is to produce more potent products requiring a higher level of containment. Nowadays, new pharmaceutical plants are usually designed and built according to the latest standards in containment. Process equipments and operation steps are designed upfront for complying with a predetermined containment level.

In most cases, the plant is not designed for a single operation but for multipurpose operation. One of the challenges of a multipurpose plant is that they are required handling a large range of products (dry and wet) in various quantities and different types of packaging. Safety data is not always readily available for the material to be handled. This problem is even more evident for pilot plants where new substances are developed.

A pharmaceutical production unit includes a number of stages involving powder handling. Process equipment such as dryers, reactors, centrifuges or mills have to be charged and discharged in a totally contained manner. A classical method for achieving a high containment level is to use an isolator/glove box. However, such installations are generally conceived for a specific operation (charging or discharging) and adapting them for other functions is either very complicated or totally impossible.

The selection of the containment philosophy is of prime importance as it will have a direct impact on the operation efficiency. For this reason, the containment technology selected should be upgradeable to higher containment level and if possible adaptable to different types of packaging.

The task is even more complex when an existing facility needs to be upgraded. The process equipment is usually (reactor, dryer, etc.) not designed for high contained operation and the lack of space or height makes it difficult to implement standard containment technology.

A risk management approach must be implemented when selecting the suitable technology. In case of handling very potent materials, it is required to consider various scenarios including the possible failure modes of the containment systems.

For instance, the designs of many containment systems (flexible bag technology, spilt valve, etc.) are based on the concept of primary containment (single barrier). If the system fails, containment is no longer guaranteed.

As an example, an approach of risk management is already applied in the European safety directive for the prevention of explosion (ATEX Directives 94/9/EC, 99/92/EC) where four levels of risks are considered. For each level, the degree of protection required is clearly indicated.

In the following table, an analogy is made between this approach and the requirement of containment depending on the product toxicity. In this case, the four levels of risks are determined by the OEB (Occupational Exposure Band) of the products.

Table 1: Analogy between ATEX and OEB

Level of risks	Safety against explosion ATEX	Containment OEB	Protection level	Containment required
No risk	No zone No presence of an explosive atmosphere	OEB 1 Product not toxic	No protection required	None
Low risk	Category 3, Zone 2; 22 Explosive atmosphere not to be expected or occasionally during normal operation	OEB 2-3 Almost non-toxic, less toxic	One level of safety required for normal operation.	Primary containment
High risk	Category 2, Zone 1; 21 Explosive atmosphere to be expected during normal operation	OEB 4 Toxic	Level of safety required for normal operation and failed operation.	Primary and secondary containment
Very high risk	Category 1, Zone 0; 20 Explosive atmosphere present continuously or frequently	OEB 5 High toxic	Double redundancy of safety in case of failed operation.	Two levels of secondary containment

Considering this safety concept, technologies offering only a single barrier (primary containment) should not be used for highly toxic products without the uses of a secondary

containment such as an isolator, even when such technologies could reach the required level of containment in normal working conditions.

2.3 Safety

In the pharmaceutical industry, it is often necessary to handle powder with a low minimum ignition energy (MIE < 10 mJ) or load powder in the presence of solvents. Accidents resulting from these tasks are unfortunately still too frequent in production plants.

Despite the high incidence of accidents, the dangers related to powder handling are not as well controlled as those related to the handling of liquids, probably because problems related to powder handling are much more complex due to the particular nature of powder. Many parameters must be taken into consideration in a hazard assessment: Firstly, the sensitivity of the dust atmosphere to ignition (particle size distribution, specific surface area, moisture content, resistivity of the powder in bulk, turbulence, concentration of powder and oxygen, design of the equipment, etc.), secondly, the incendivity of the presumed ignition source (flames, sparks hot surface, electrostatic discharge, friction, impact, etc.).

The new European ATEX regulation (Directive 94/9/EC, 1994 and Directive 1999/92/EC, 1999) have started to sensitize the concerned parties and force the persons in charge of production to carry out hazard assessments that are much more detailed and comprehensive than they used to be. Certain types of high-risk operations will probably no longer be allowed in the future, for example charging a reactor with powder through an open manhole.

As clearly stated in the directives, the employer shall take technical and/or organizational measures appropriate to the nature of the operation, in order of priority and in accordance with the following basic principles:

- The prevention of the formation of explosive atmospheres, or where the nature of the activity does not allow that,
- the avoidance of the ignition of explosive atmospheres, and
- the mitigation of the detrimental effects of an explosion so as to ensure the health and safety of workers.

These measures shall, where necessary, be combined and/or supplemented with measures against the propagation of explosions and shall be reviewed regularly and, in any event, whenever significant changes occur.

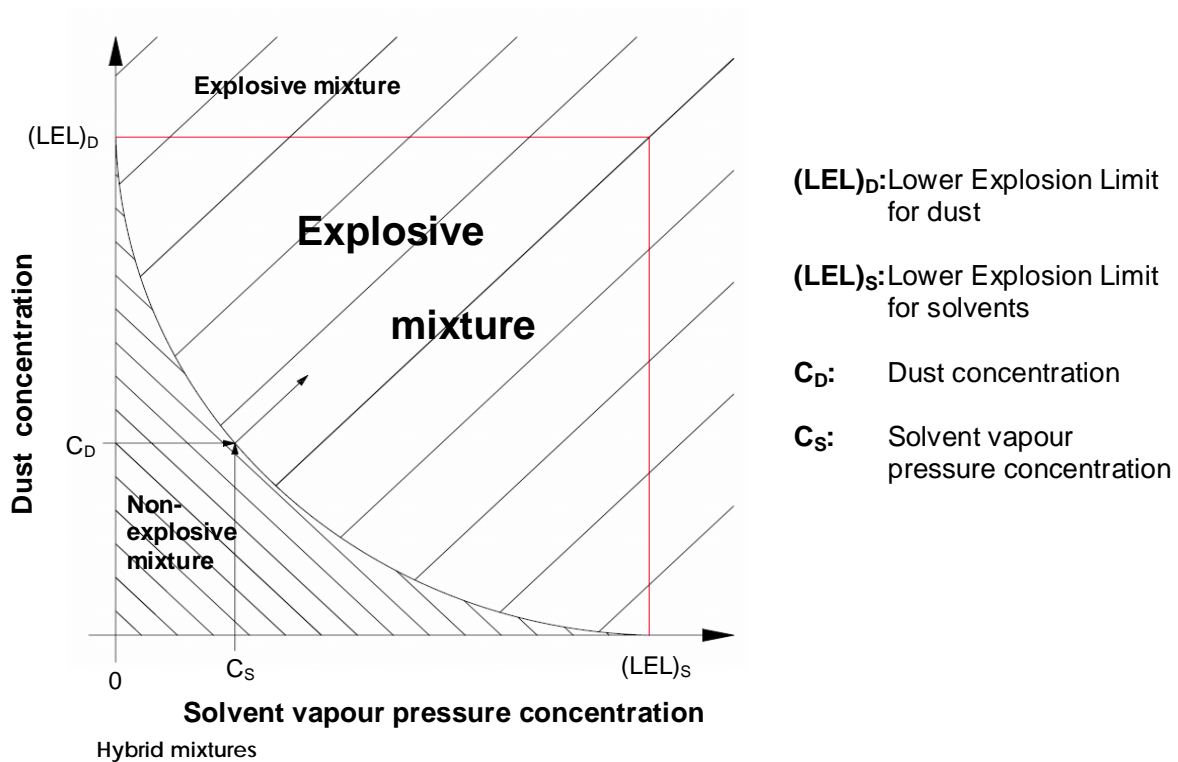
One of the major source of accident in production area is when powders are handled in the presence of solvents (charging reactors and dryer, emptying centrifuge, cleaning activity,...)

For instance, when charging powder into a reactor filled with solvent, the dust cloud will become mixed with the solvents vapours and will form a hybrid mixture with the following characteristics:

- Even if the concentration of both components, the dust cloud and the solvent vapour lie below their own lower explosion limit, the hybrid mixture as a whole may be within the explosive range.
- The MIE of the hybrid mixture usually lies between the MIE of the components. Since the MIE of the solvent vapour is usually lower than the MIE of the powder, the MIE of the hybrid mixture is usually much lower than the MIE of the pure powder, even if the flash point of the solvent is above ambient temperature

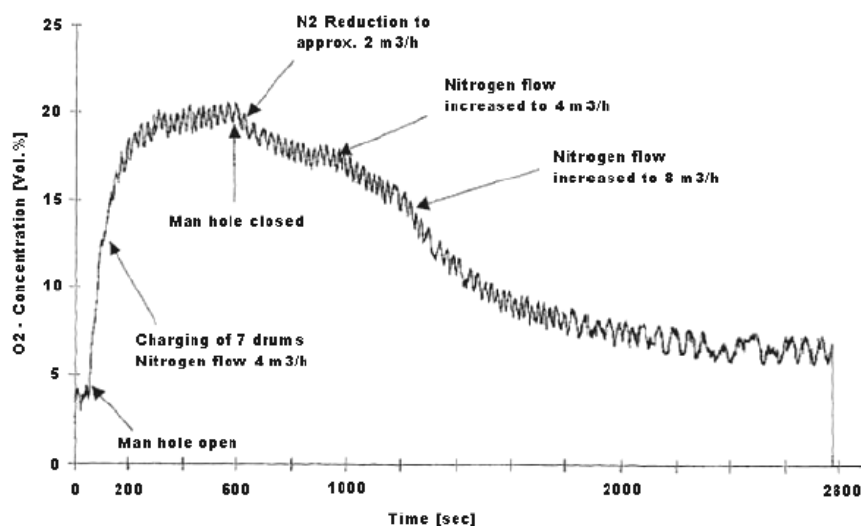
If the gas or vapour concentration is below 20% of the lower explosion limit, the effect of the gas or vapour can be neglected (BGR 132, 2003). This means that the MIE of the pure powder represents the proper value.

A concentration of 20% of the lower explosion limit is usually reached at a temperature of about 30 to 40 K below the flash point for most common solvents. Thus, this "30 to 40 K rule" can be used as a rule of thumb to judge the probability of the formation of a hybrid mixture (i.e. Methanol FP= 11°C/T/20%LEL=-19°C).



In the case of hybrid mixture, even ignition source with low energy (i.e static electricity) will become effective.

When powders are charged into a reactor filled with flammable solvent in an open way, it is very difficult to prevent explosive atmosphere. Experience shows that when opening any access port of the reactor the inert atmosphere will no longer be maintained within the reactor.

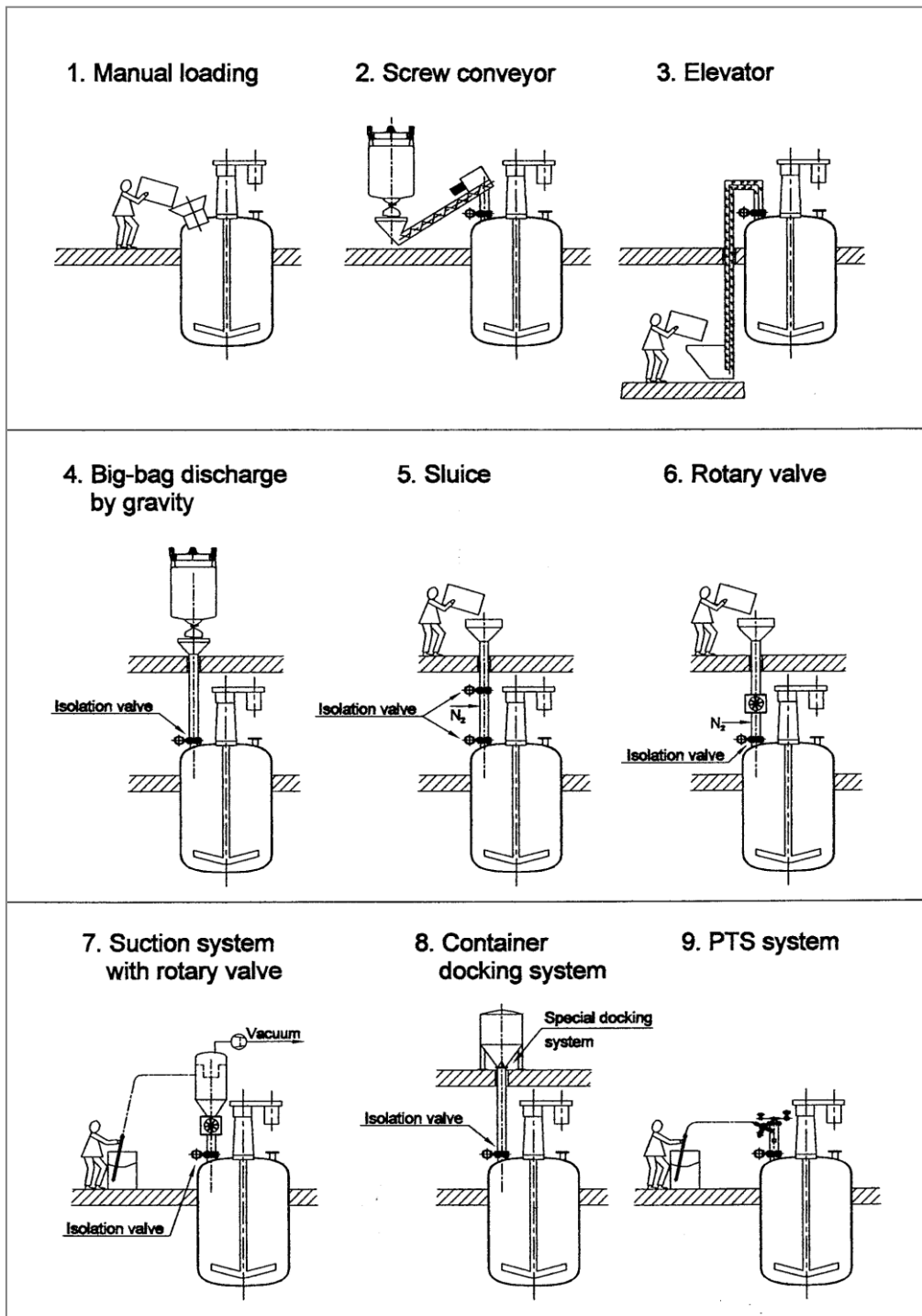


Oxygen intake during open charging through a manhole

For this reason, the transfer of powder into a flammable solvent should always be performed under inert conditions.

The transfer of powder, into the preinerted vessel, should be therefore carried out with the help of a lock system.

Most commonly used systems are shown in the next figure with their various characteristics summarized in the following table.



	Manual Transfer	Screw conveyor	Bucket/Chain conveyor	FIBC discharge	2 Valve system	Rotary valve	Vacuum transfer with lock	Docking station for Containers	PTS- System
Prevention of explosive atmosphere									
Transfer to closed reactor, inerting possible	-	+	++	++	++	++	+	++	+++
Entrainment of air with powder transfer highly improbable	-	++	-	+	+	+	+	+	+++
Entrainment of air within bulked product excluded	-	-	-	-	-	-	-	+	+++
Repeated inerting not required for transfer of large quantities	-	++	-	+	+	+	+	+	+++
Inert atmosphere maintained after transfer	-	+	-	+	+	+	+	+	+++
Diffusion of flammable gases or vapours to surroundings excluded	-	+	+	+	+	+	+	+	+++
Formation of dust cloud in surroundings not expected	-	+	-	+	-	+	+++	+++	+++
Other advantages									
Required space (particularly above the reactor) low	+	+++	.	-	.	-	++	-	+++
Easy to clean	++	+	-	++	+	+	+	+	++
Mobile transfer system	+++	++	-	-	-	-	-	-	++
Transfer into pressurized systems	-	-	-	-	-	-	-	-	+++
Not depending on flow properties of powder	+++	-	+++	+	+	+	+	++	+++
GMP (good manufacturing practice) Conformity	-	+	-	+	+	+	+	+++	+++
Transfer over large distances	-	+	++	-	-	-	++	-	++
Investments	+++	+	-	+	+	-	-	-	+
Charge Moist or Solvent Wet Powder	+++	+	++	++	+	+	+	+	+++
For Multipurpose Applications	+	-	-	++	+	+	++	+	+++
Provides Manufacturing Flexibility	+	+	-	++	-	+	+	-	+++
Automated Operation	-	+	+	+	+	++	++	++	++
Environmental Health & Safety	-	+	+	+++	+	+	+	+	+++

Most transfer systems, except the PTS-System, will not prevent the oxygen enrichment within the reactor with increasing amount of powder transferred due to the air comprises within the powder. This is particularly a handicap in case of products with low bulk density and/or transfer of large amounts (volumes) of powders, which will nearly fill the total free gas space within the reactor

2.4 Productivity

Stricter safety and quality standards have pushed the industry to modify their traditional way of operation and lead them to close their processes.

In most cases, the safety and the containment of the plant have been improved by implementing closed powder handling systems but often at the detrimental of the productivity.

It is therefore important, when selecting a specific technology, to check its impact on the productivity and the flexibility of the facility as much as on the maintenance and operating costs.

Different approaches can be followed in order to optimize a production facility:

2.4.1 Process optimization

One of the major activities in a synthesis plant is to carry out reactions. By optimizing a reaction process large savings in energy consumption, production time and product quality can be achieved.

Reaction processes are usually developed and determined in R&D and pilot plant facilities. However, the cost of operation generally becomes an issue when at full scale production. For this reason, it is vital that research and production facilities work closely in order to develop the best manufacturing procedure and, if possible, use identical operating tools allowing for upscale of the production.

One important parameter influencing the efficiency of a reaction is for instance the way powder is charged into a vessel. By determining the best time of charging, the process can be improved largely. For this reason, the following parameters should be established during the laboratory and pilot plant testing.

- Optimal temperature and pressure during charging
- Speed of addition
- Sequence of addition (solvent, powders, etc.)
- Agitation speed

The technology used for charging powders into reactors should therefore permit the addition of powder in a controlled manner and under variable process conditions.

However, powder is still charged nowadays, in most cases, in empty reactors or when they contain cold solvents. The main reason is that the various technologies used are based on gravity operation and don't allow the charging of powder into reactors under pressure or temperature conditions mostly due to safety reasons and equipment design.

The disadvantages of charging an empty reactor, i.e. without the presence of solvents are various:

- Risk of damaging the agitator seal or the agitator itself due to the large amounts of solids at the bottom of the reactor.
- Damage to the reactor lining due to the abrasion of the powder.
- Long mixing time and problems with product homogenization due to the formation of agglomerates.
- High static creation by the introduction of powder in dry conditions.

2.4.2 Process isolation

In order to comply with the safety and GMP requirements, separation of process and operation steps should be guaranteed at all times. Process equipments should be isolated, from the outside atmosphere, during filling and discharging operation.

Most powder handling systems are not designed to be pressure proof or explosion proof, yet they can be directly connected to other equipment, which may be under pressure, contain an explosive atmosphere and run at high temperatures. In this case, as there is no physical barrier between the two systems during the powder loading and, due to the direct connection between systems, there is a potential risk of an explosive atmosphere developing in the powder-handling zone or corrosion occurring, for instance, in the charge chute in the event of a corrosive atmosphere being present.

2.4.3 Process linking

One way to improve productivity, safety and containment at the same time is to interconnect production equipments in a closed way (i.e. discharging a centrifuge directly into a dryer or a reactor). Unfortunately, such operations are often not possible due to the layout of the equipments and production constraints.

2.4.4 Flexibility

Nowadays, a pharmaceutical facility should be designed for multipurpose operations in order to adapt quickly to the market requirements. The design of the production unit should allow fast changes of the process by using mobile and modular technologies.

The powder handling technologies should be able, if possible, to handle different types of packaging (drum, bag, Big-Bag, etc.) and at the same time should allow the transfer of small and large quantities of powder.

Usually, powder handling systems based on the gravity concept are mostly dedicated to one type of operation and designed for a specific recipient (container, small bag, plastic bottle, etc.). A separate dispensing area is often required in order to empty the original packaging and fill the correct amount of powder into these specific receivers. Such operations are costly and time consuming and don't necessarily offer the flexibility required in a multipurpose plant.

2.4.5 Process Upgradeability

A multipurpose plant should be designed with a certain degree of upgradeability in order to be able to quickly adapt to the frequent change of processes. Different levels of containment are usually required in a production facility depending on the process step and the characteristics of the products (toxicity, MIE, etc.).

The powder handling technologies should be designed in order to handle powders with various levels of containment. We can see, nowadays, a clear trend from API manufacturers to produce more potent products requiring a higher level of containment (OEB 5 products).

3. New concept for a production unit: Active loading

In an effort to overcome these various problems, a solution was developed to isolate the equipment during the loading phase, to transfer powder in a contained manner and at the same time offer the required flexibility for improving the operation.

This solution is based on the concept of transferring powder in an active way without the use of gravity. It is thus possible to view the handling of powder like the handling of liquids.



The heart of this concept is the PTS (Powder Transfer System, patented), which uses a source of vacuum and a source of pressure to transfer powder. This system can be used during various stages of the production, e.g. to handle raw materials, to charge or discharge process equipment and to package the finished product.

Powder can be transferred from almost any receptacle (drum, big bag, container, process equipment, etc.) and over long distances, thus allowing for more flexibility when designing

production units.

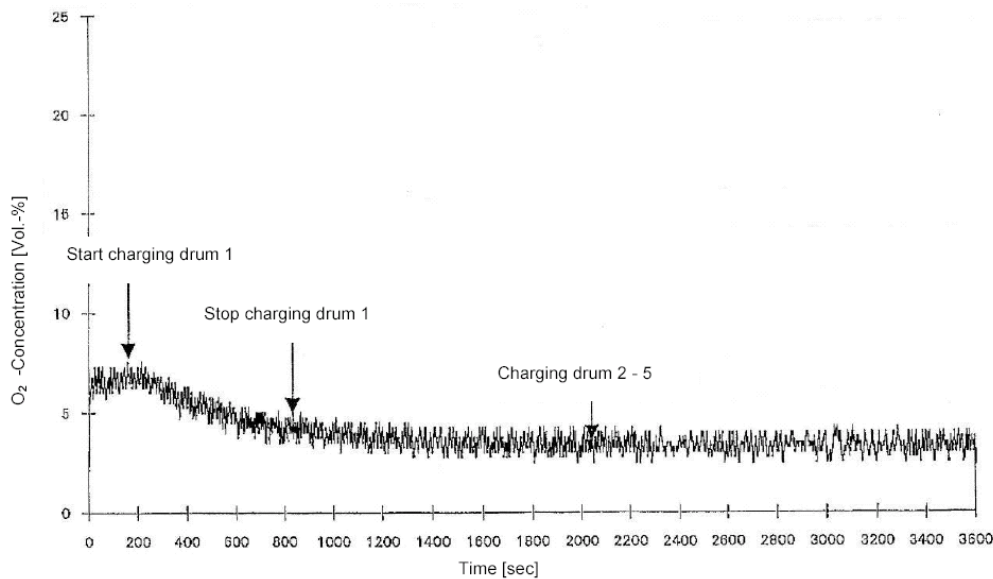
PTS Powder Transfer System installed on a reactor

The logistics of the powders in the production plant can be simplified, e.g. by leaving the raw materials on the lower floor and then transferring them directly into the production equipment. As a result, it is possible to eliminate the powder handling zone above the receiving vessel as well as the elevators. In certain cases, one can even avoid having to build an entire floor.

The operating principle of the PTS is as simple as it is effective. Powder gets sucked into the PTS chamber by vacuum. A flat filtration membrane, installed in the upper part of the system, ensures that no fine product particles can enter the vacuum line. As soon as the chamber is full, the cycle is reversed and powder is discharged into the receiving vessel by compressed gas. At the same time, the filter membrane is cleaned by the reverse flow of compressed gas, thus ensuring its optimum performance.

The PTS, designed for pressure, is directly installed on the receiving vessel, which it can isolate during the loading phase.

One of the major advantages of this technology is that it makes it possible to remove the air from the powder and to keep the receiving vessel inert while loading the powder by using, for example, nitrogen to discharge the PTS chamber.



Oxygen concentration while charging via the PTS Powder Transfer System

It is, therefore, possible to safely fill powder into a reactor, which contains solvents or is pressurized, without risking explosions or dangerous gas leaks.

The system uses practically absolute vacuum to transfer powder, which takes place in dense-phase flow, making it possible to handle powder with very different characteristics (fine, wet, sticky, moist, etc.), and at low speed (1-3 m/s), in order to preserve the characteristics of the product and to limit electrostatic charges.

Thanks to the design of the equipment and its particular transfer characteristics, it is possible to eliminate explosions even when transferring powders with very low minimum ignition energies (< 1-3 mJ).



PTS Powder Transfer System

The PTS uses only a limited amount of gas for the transfer. It is, therefore, easy to suck powder directly out of a large container (big bag, container, dryer, etc.) without having to install a complex fluidization system or a device to proportion the powder (sluice, etc.). A simple connecting piece, attached to the lower part of a container or big bag emptying station or located directly at the outlet of the equipment to be emptied, makes it possible to transfer powder with the PTS.

Problems regarding containment can now be avoided easily by permanently connecting the different pieces of process equipment to each other (e.g. connecting a centrifuge to a dryer or reactor). It is, therefore, no longer necessary to invest in expensive containment systems to charge and discharge powder.

The PTS can also transfer liquid, which makes it easy to clean the system including the attached process equipment in place. The system can be cleaned and dried fully automatically and at no additional cost.



This approach provides a lot of flexibility when designing a production unit, because the PTS is very adaptable. It can be used to empty a wide variety of receptacles, making it possible to transfer small quantities of powder as well as large ones and to adapt the speed of transfer to the requirements of the process. Dispensing precise amounts of powder into process equipment is possible without the use of complex control systems.

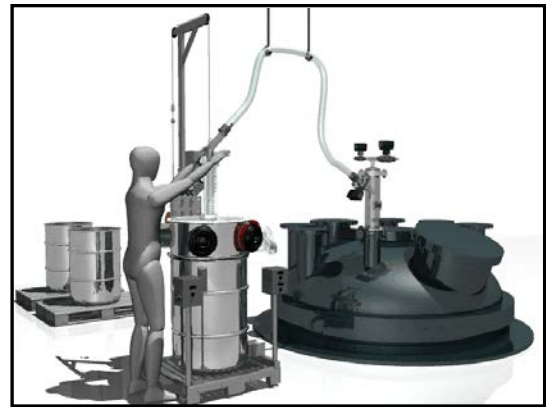


It is easier to control the manufacturing process because powder can be added at any stage of the reaction in a controlled and perfectly safe way. The PTS can solve a multitude of problems, especially when combined with the appropriate tools.

Most powders are delivered and stored in drums. Emptying a drum containing a toxic product in a contained manner without any contamination is not an easy operation.

The DCS (Drum Containment System) was developed to be used in combination with the PTS (Powder Transfer System) to discharge drums in a fully contained manner and to transfer powder directly into process equipment without any contamination.

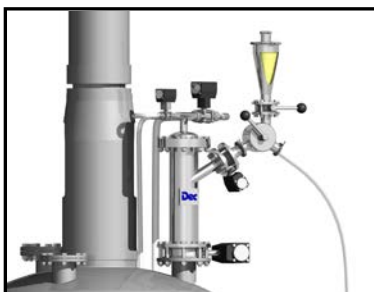
The DCS consists of a cylindrical transparent glove box with two glove ports. A suction lance, connected to a PTS and introduced from the top, is attached to the glove box with a bellows in order to seal the system.



DCS – Drum Containment System

The entire system is attached to a frame, which allows the glove box to be lifted and lowered over the drum. The operator can open the drum with the gloves and empty it with the suction lance in a totally contained manner.

Combining the DCS with the PTS technology offers many advantages compared to traditional isolator systems:



SCC – Single Charge Container

- Very compact and mobile system, can be installed at a few meters distance of the receiver to be charged
- High containment level ($< 1 \mu\text{g}/\text{m}^3$) and the possibility to charge equipment under inert conditions (e.g. a reactor containing flammable solvents)
- Economical solution
- High flexibility, adaptable for emptying various types of drums and bags
- Ergonomic system with good visibility into the drum during the operation

It is sometimes necessary to charge a reactor or crystallizer with small amounts of powder (catalyst). For this application, a small receiver SCC (Single Charge Container), with a manual valve installed at the bottom, was developed. The SCC can easily be connected to the inlet of the PTS by rapid couplings or a special valve. One filled, this receiver is connected to the PTS

and is emptied by suction from the PTS. The receiver is equipped with a filter at the top, which avoids having to place the container under vacuum and allows it to be emptied completely. This technology makes it possible to have only one zone for powder handling, from which various receivers (e.g. a reactor) can be charged or production equipment (e.g. a dryer) discharged and transferring the powder to a special packaging area. The savings in terms of space and equipment are substantial.

Production validation and quality assurance are among the many challenges in pharmaceutical productions. Sampling is one of the best methods to meet these requirements. Sometimes it is difficult to take a sample directly from a piece of process equipment because of its design (agitator, etc.) or its lack of accessibility (confined zone).

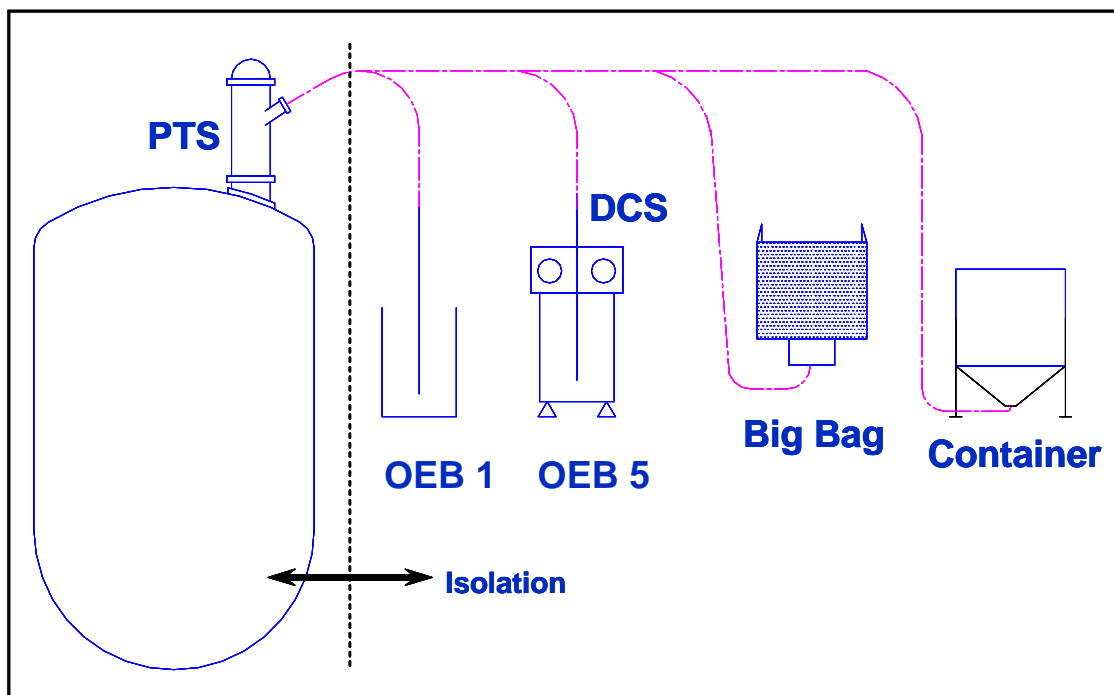


The MPTS (Micro Powder Transfer System) makes it possible to take online representative samples of powder directly from the process equipment at each stage of the production.

The MPTS allows samples to be taken from different types of equipment (dryers, mixers, packaging systems, etc.) without using any mechanical device, and transferring the samples, while preserving their homogeneity, to a separate, safe and easily accessible location. It is, therefore, possible to take samples from machines located in areas with difficult or limited access (no personnel allowed) as well as to sample toxic powders in a contained manner.

MPTS – Micro Powder Transfer System

Packaging an intermediate or final product is one of the delicate tasks of a production unit. The selected systems must allow some degree of flexibility with regard to the different types of packaging, while guaranteeing an appropriate level of containment and precise portioning.



The proposed technology is flexible to one's liking. It is possible to fill various types of containers in a precise and contained manner. The DCS (Drum Containment System) allows charging drums or big bags without the risk of contamination ($< 1 \mu\text{g}/\text{m}^3$). The systems are very compact and can even be mobile.

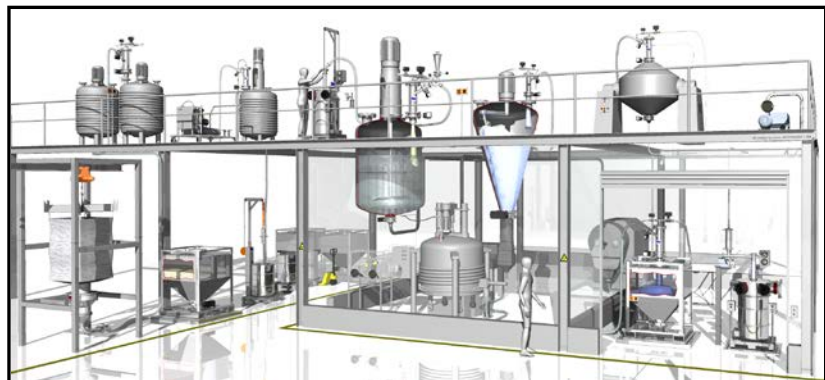
The powder that needs to be packaged is directly transferred from the process equipment to the dispensing area. It is thus easy to centralize and delimitate the packaging area.

4. Conclusions

Due to the increasingly difficult economic situation, pharmaceutical industries face many challenges when designing new production units.

Production units must remain very flexible in order to be able to adapt quickly to changes in the market and to conform to the very strict safety and quality control standards. The operation and maintenance costs must be kept to a minimum.

It has become obvious that powder handling is an unavoidable element in a production facility and that the choice of the appropriate technology can guarantee the success of a new production plant.



Active loading