

How to make tablets from potent APIs

Part 1: Containment Fundamentals

Introduction

When talking today about solid dosage form production, often containment immediately becomes one of the issues. Why? The first reason is that APIs are becoming more and more potent: meanwhile more than 50% of all NCE (New Chemical Entities) are classified potent (OEL < 10 µg/m³). Secondly, health and safety authorities all around the world are putting more focus on the protection of operators dealing with these substances. The third reason is that suppliers of various hardware components have developed a huge variety of containment solutions, making it difficult to decide which is best, even for experienced people.

Before we look at the factors defining the required containment levels, and discussing the possible hardware solutions, some fundamental thoughts about containment need to be covered first.

Regulatory situation

“It is the first duty of the employer to protect (the health) of his employees.” Even though the regulatory situation differs from country to country, the above statement (taken from the UK COSHH rules) should be seen as general guidance when handling potent substances.

In fact, approximately 30% of all people in western societies will develop some form of cancer during their lifetime. If one of these had been exposed to a carcinogenic substance, whilst working for a pharmaceutical company, there is the potential for a legal claim against the company. This could result in high cost compensation and in very bad publicity, unless the company can prove that the employee had been protected using best available technology.

Whereas the UK COSHH rules show a clear hierarchy of control measures:

1. **Elimination at the source**
2. **Substitution with a less hazardous material or form**
3. **Reduction of the quantity below critical limits**
4. **Engineering controls to prevent intolerable operating staff exposure (contained handling)**
5. **Administrative controls**
6. **Use of Personal Protection Equipment (PPE)**

In many other countries no legislation enforces this hierarchy. Most of the western countries will monitor the conditions under which operators have to work in the countries from which they import as it is seen as highly unethical to support practices that create health and safety risks in other areas of the world.

There are good reasons for this order of preference, especially that PPE should only be used as a last resort (for maintenance; for necessary, but unforeseen interactions; or if any other method further up in the hierarchy has been considered without success). Why is this? Firstly, PPE only protects the operator. The hazardous substance is not contained, which means that the associated problems are increased: changing of filters, cleaning of rooms and equipment, inside and outside, become major containment issues.

Additionally, depending on the PPE system used, the levels of protection are limited. For systems taking the air from the room via a filter system, the best filters (P3 according EN 149) offer NPFs (Nominal Protection Factors) of 30. This means that if the dust concentration in a room is 3 mg/m³ (typical for open production), at best the concentration inside the system will be 100 µg/m³. Additionally, the lifetime of the filter element is limited because of the high dust loading.

The situation is different if air-fed systems are used. These systems can provide better protection levels, but there are still some areas of concern. The performance of these systems is very operator-dependant and in most countries it is not acceptable to put the responsibility for his health (or even life) into an operator's own hands. The working conditions inside an air-suit are unpleasant: hot, humid with poor visibility and limited movement. This results in low levels of operator efficiency, and the need to take frequent breaks, reducing efficiency even further.

It is also important to notice the hidden costs associated with those systems such as:

- **large number of systems required**
- **lifetime of suits and filters is limited**
- **cost for clean air supply**
- **requirement for extra changing and storage areas**

These areas are most critical for the performance of the systems. After working in the contaminated area, the outside of the suit is contaminated with API. This contamination needs to be removed, which can be done either by air or wet showers. Whichever method is chosen, the remaining residuals, especially for very potent substances such as hormones or oncology products, can still be critical.

The effectiveness of air suits needs to be understood. It is a common misconception they provide total protection, but in reality typical NPF and APF (Applied Protection Factors) are:

Equipment Item	NPF	APF
Air-Fed Suit	10,000	200
Air-Fed Half Suit	2,000	100
Air-Fed Hood	2,000	40
Filter Air Hood	500	40

APFs represent the reality of daily operation. Using the same example as above, this means that if the dust concentration in a room is 3 mg/m³, at best the exposure level for an operator wearing a full air-fed suit will be 15 µg/m³.

Containment risks

During most of the manufacturing process, the APIs are inside machines or vessels which are more or less airtight. The main risk of material escaping into the environment exists whenever a connection between those pieces of equipment needs to be made or broken, when a sample needs to be taken, and when the machines need to be cleaned at the end of a manufacturing campaign. Before the risks for the operators' health are discussed we should also spend some thoughts on the risks of cross contamination. Even in the best designed multi-product facilities cross contamination will happen. The critical question is how much cross contamination is acceptable and how it can be ensured that the real levels of cross contamination are always below the acceptance limit.

Cross contamination

How much cross contamination can be allowed is mainly dictated by the potency of the products handled. The most common definition of an acceptable level is: In the maximum daily dose of product 2 only 1/1000 of the minimal daily dose of the active of product 1 should be found. If we compare now Paracetamol tablets (4000mg max daily dose) with typical oral contraceptives (containing 0,02 mg as a maximum daily dose) we see that the acceptable level of cross contamination in case 2 is by a factor of 200.000 higher than in case 1. Common ways to reduce the level of cross contamination in multi product facilities include separate production rooms, air locks and pressure cascades. These are fine for less critical products but when highly potent substances are handled, strict containment is the only way to protect both the operators' health and the other products.

How much containment is required?

In an ideal world operators would not be exposed to a single molecule of a harmful substance, but in the real world, this is simply not possible. Three main factors dictate how much containment is required and, therefore, which method of containment is best: the nature, especially the potency, of the API handled is of paramount importance; the type of process to be executed; and lastly the working regime of the operators.

The product

The potency of a substance is, in most cases, characterized either by the OEL (Occupational Exposure Limit) or by the ADI (Acceptable Daily Intake). The ADI describes the absolute amount of a specific drug substance that an operator can absorb without any negative effect on health. The OEL describes the maximum concentration of a drug substance which can be tolerated in the air of the production room, without any negative effect to the health of the operators. For established substances, these values are listed in textbooks such as ISBN 07176 2083 2 EH40/2002 OEL 2002 & ISBN 07176 2172 3 EH 40/2002 Supplements 2003. According to those, the OEL for Paracetamol is 10 mg/m³, while the OEL for Ethinyl estradiol is 35ng/m³. It is important to understand that these values are based on certain assumptions. Also, the values might change during the lifecycle of a substance especially after more toxicological data is generated. If an OEL for a substance cannot be obtained from the literature, the value can be determined as follows:

$$OEL = NOEL [mg/(kg \times day)] \times BW [kg] / V [m^3/time] \times SF1 \times SF2 \times \dots$$

with:

- **OEL = Occupational Exposure Limit**
- **NOEL = No Observable Effect Level**
- **BW = Body Weight**

- **V** = Breathing Volume
- **SF** = Safety Factor

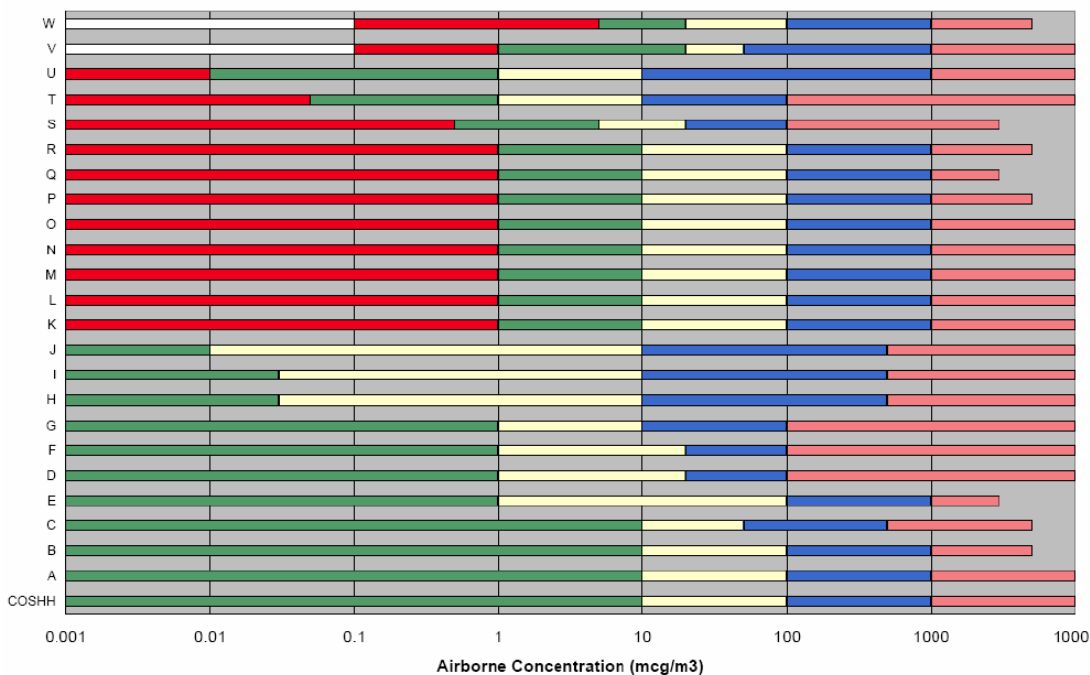
ADI and OEL are interconnected by the typical breathing volume of an operator (normally estimated as 10 m³/shift). Therefore;

$$ADI = OEL \left[\frac{\text{mcg}}{\text{m}^3} \right] \times V \left[\frac{\text{m}^3}{\text{day}} \right]$$

$$ADI = 10 \times OEL [\text{mcg/day}]$$

$$ADI = \frac{NOEL [\text{mg}/(\text{kg} \times \text{day})] \times BW [\text{kg}]}{SF_1 \times SF_2 \times \dots}$$

Additionally, it is common practice to describe the potency of a drug substance by an easy categorization system classifying all potent substances from 1 (less potent) to 5 (most potent). This allows production equipment to be classified as suitable for the production of a class X compound, plus it easily shows to operators the potency of the substance. However, when talking about this simple classification system, two important facts need to be considered: it is not totally universal, as the attached diagram shows; and nearly every company has its own classification system.



It also does not take into account the dilution of the API by excipients. The handling of a mixture containing 80% of a 'class 3 API' can demand higher containment levels than the handling of a mixture containing 5% of a 'class 5 API'.

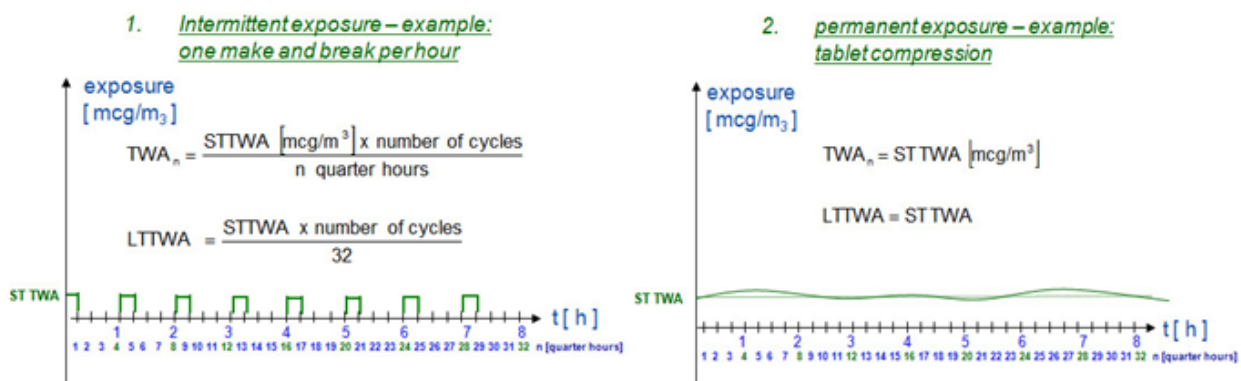
As we will see in the following chapters, the concept of production lines suitable for the manufacturing of all class x compounds can be questioned. It oversimplifies the situation, not taking into consideration dilution (not all substance handled is pure API, especially when dealing with very potent substances often a large percentage of the mixture is excipient), the real number of operations, or also the fact that operators might not be present all time.

The equipment

Suppliers not specialists in the field often try to promote 'their containment equipment' with claims such as “3 µg/m³”, “better than 1µg” or even worse “OEL 2 µg/m³”. All of these claims are meant to describe the containment performance of equipment such as extraction booths or containment valves. While the last claim obviously is wrong (OEL is a product-related number, it only has the same unit as the containment performance of a piece of equipment), the problem of the other claims is that the test conditions are not defined. This makes it extremely difficult to compare figures obtained by using different test materials, different samplers, different sampler positions or different analytical procedures.

After inventing the split valve technology, GEA Buck Valve again took the lead to form (under the umbrella of ISPE) an expert working group, consisting of experts from pharma companies, engineering companies and containment equipment suppliers. This group developed a guideline <http://www2.ispe.org/eseries/scriptcontent/orders/ProductDetail.cfm?pc=IGPGAPCUS> in which all of the variants discussed above are defined. The accepted test procedure uses Lactose of a defined grade (other substances are possible), uses the equipment in a defined environment (humidity, temperature, number of air changes), and places the defined samplers in specific positions. The test includes performing the intended task, and collecting air (via the filters of the samplers) for 15 minutes. Analyzing the filters gives the quantity of lactose in a measured amount of air, which is the containment performance of the equipment. As the average of 15 minutes is taken, this performance is called STTWA (Short Term Time Weighted Average). It is important to note that the total amount of powder escaping is measured. If dealing with potent APIs, often only a small percentage of a powder mixture is active, while the rest is excipient. The LTTWA (Long Term Weighted Average) is defined as the containment performance over a longer period of time, for example one shift of 8h.

The diagram shows two different scenarios



It is important to distinguish if there is an intermittent exposure as shown on the left side generated e.g. by the docking of a container with raw materials to a fluid bed with subsequent operation of the fluid bed, or a permanent exposure as shown on the right side e.g. by a tablet press which is not totally tight.

The Operator

The most important numbers to describe the exposure of the operator are ROI (Real Operator Intake) and RDI (Real Daily Intake). These numbers describe the amount of API which gets into the body of the operator while being for a certain period of time in an area with a certain airborne drug concentration. If we know the breathing rate of the operator, and the dust concentration in the room, then the drug uptake can be calculated. For example:

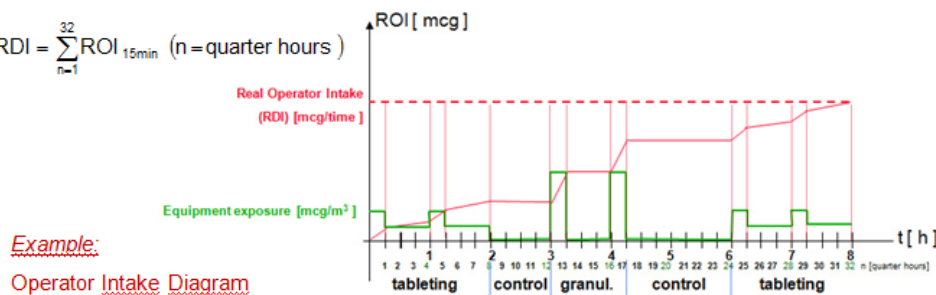
How to calculate the Real Operator Intake (ROI)

$$ROI_{15min} = ST TWA \times V_{15min} \times dilution\ factor \quad \left(V_{15min} = \frac{10m^3/day}{32\ quarter\ hours/day} \right)$$

$$ROI_{15min} = ST TWA \left[mcg/m^3 \right] \times 0,3125 \frac{m^3}{15min} \times dilution\ factor$$

How to calculate the Real Daily Intake (RDI)

$$RDI = \sum_{n=1}^{32} ROI_{15min} \quad (n = \text{quarter hours})$$



If the actual RDI is less than the drug specific ADI, the situation is fine. If the RDI exceeds the ADI, measures must be taken to improve the situation. In our example the most effective way would be to upgrade the granulator by a loading/unloading system with a better containment performance.

Conclusion of Fundamentals

This visualisation helps the concept to be easily understood. For real situations of course, a detailed risk analysis needs to be done in order to judge the containment performance of an existing installation, or to select the appropriate equipment for an upgrade of an existing facility, or the design of a new facility.

GEA Pharma Systems not only offers the largest variety of hardware solutions for contained materials transfers, but also unrivalled experience in identifying the most appropriate solution, based on a containment risk analysis.

Part 2: Selection of appropriate Production Technology

A typical tablet production consists of the following steps

- Dispensing of API and Excipients
- Milling of Raw materials in order to destroy lumps
- (Wet) Granulation with subsequent Drying
- Dry Milling
- Addition of Lubricants
- Tablet Compression
- Coating
- Primary and secondary packing

The selection of the overall material handling system for potent APIs is of paramount importance as it determines more than any other aspects the containment performance of the entire installation. There are fundamentally two choices: systems based on stainless steel or disposable systems.

IBCs (Intermediate Bulk Containers) with split butterfly valves are the most commonly used material handling systems for dealing with potent APIs: the entire material required for a batch is loaded, e.g. under a laminar flow booth, into the IBC in the dispensing area. This IBC is then moved into the granulation area where it is docked using a split butterfly valve connection to e.g. a discharge station. The raw material is loaded either by gravity (if the room height allows) or via vacuum conveying into the granulator. A mill for breaking lumps should be integrated in between.

Split Butterfly Valves

Split butterfly valves offer a proven solution for make and break connections. They are available in different performance levels.

[An overview can be found here.](#)

As a disposable solution [Hicoflex™](#) which allows the excipients to be handled in a conventional way, can be used. The API can be weighed inside a glovebox and, via a funnel, be transferred into a Hicoflex™ bag below. Afterwards both containers are connected via an integrated mill to the granulator infeed.

Granulation

For granulation various options exist ([for more information please follow the link to comparison paper](#)). If potent APIs are used typically only a small percentage of the formulation is API. These low dose recipes are not well suited for dry methods, such as roller compaction, as first these machines are very difficult to build in a contained way and there are quite often problems achieving an even distribution of the API. Therefore wet granulation methods should be preferred. Here there are four main options:

1. Integrated line consisting of a high shear granulator and a fluid bed
2. Fluid bed spray granulator
3. Continuous granulation and drying
4. Single pot processing

The advantage of option 1 is to combine the most efficient granulator with the most efficient dryer to achieve high throughput can be realized. Additionally the high shear granulation process avoids any issues with material separation which can be challenging when micronized APIs are used. Another advantage is the robustness of the granulation process which allows, for example, the opportunity of compensating for fluctuations in raw material quality by adjusting the process parameters. The downside of course is the configuration of the equipment which, during product changeover will demand a longer downtime than other. This option also requires the use of a high quality, high-shear granulator. For example systems with good impellers ensure a fast and even distribution of the granulation liquid. This avoids subsequent problems with uneven drying and extended time needed for the milling of the granules after drying.

Fluid Bed spray granulation is a Single Pot operation which is a huge advantage when handling potent substances. The process also creates material with high inter-granular porosity that demonstrates excellent compression behavior. Using the FlexStream™ system developed by GEA Pharma Systems, granules also show excellent flow properties that are most important for a homogenous filling of the dies during compression. For cleaning the filters can be wetted down and taken out with minimal risk of contaminating operators or environment. The remaining part of the processor can be cleaned in place.

Continuous lines such as GEA's [Consigma™](#) offer a good alternative to conventional batch systems. The only potentially problems are: 1) that the majority of existing recipes have been developed for batch machines, and; that for the existing continuous systems an automatic cleaning system is not yet proven. Continuous systems do, however, offer significant advantages so these should be closely watched for future developments.

The ideal solution for the granulation of potent API is offered by the [Single Pot Processor](#). It combines the process advantages of a high-shear granulator with a minimal surface area and the built-in possibility of cleaning in place to offer an extremely fast change-over.

After granulation the outer phase needs to be added. This is easiest if the dry granules are discharged via an integrated dry mill into an IBC. After the addition of the outer phase a homogeneous mix is achieved by tumbling the IBC in a container blender. This IBC can also be used to feed the tablet press.

Tablet Compression

When dealing with highly potent substances, compression is probably the most challenging stage of the tablet manufacturing process.

The main reasons are:

- The complex mechanical design and construction of the inside of a tablet press.
- The continuous flow of materials into and out of the press.
- The need to clean a very complex system in case of product change-over, including upstream and downstream equipment.
- The multiple interfaces between the tablet press and its environment (air inlet, tablet outlet, powder inlet, dust extraction), each requiring a contained interconnection.
- The need for frequent tablet sampling for IPC – either manually or automatically.

For compression of potent materials GEA's [MODUL™](#) tablet press offers an unbeaten solution. The key feature of the MODUL™ concept is the Exchangeable Compression Module (ECM). The ECM is a completely sealed box; it contains all product-contact parts and is easy to remove from the press.

Depending on the product and production requirements, it can be constructed in a C (normal Containment or dust-tight) or an HC (High Containment) execution. For product and/or format change it can easily be removed from the press and be replaced by a second, already prepared ECM. While the press is running again, the contaminated ECM can be cleaned in a safe remote area: the ECM is cleaned manually off-line, which significantly reduces the machine change-over time ... Read more about [High Containment in tablet Compression](#).

Case stories

Over recent years several companies in India have used the experience and technical excellence of GEA Pharma Systems when installing containment systems for highly potent compounds. These include:

Zydus Cadila - Oncology solid dosage formulations;

- Single Pot Processor – UltimaPro™ 75 & UltimaPro™ 10 (for R&D)
- Material Handling Solution: includes IBCs with Buck® MC 100 valve, Vibroflow™ & blending prism, Hicoflex® for discharging API from Isolator & charging into Single Pot Processor, IBC filling station at discharge of Single Pot Processor, Post Hoist Blender and Buck® MC Valve on Courtoy™ Tablet compression, IBC wash station, WIP drain frame.
- Tablet compression machine MODUL™ P with HC ECM

Cosmas - Oncology Solid dosage formulations

- Flexstream™ fluid bed size 3 in 10 bar execution
- Material Handling system consisting of 100 L IBCs with Buck® MC 100 Valve, Vibroflow™ & blending prism, IBC filling station at discharge of Fluid bed processor, Post Hoist Blender, Buck® MC Valve on Courtoy™ Tablet compression, IBC wash station, WIP drain frame.
- Tablet compression machine MODUL™ P with C-ECM

Natco Pharma - Oncology Solid dosage formulations

- Integrated line comprising of PMA™ 150, integrated wet mill, wet product transfer line from High Shear Mixer to FBD, Fluid bed processor Flexstream™ size 3, Integrated Dry mill & Vacuum transfer system for dried granules from FBP to IBC
- Material Handling Solution: IBCs with Buck® MC 100 valve, Vibroflow™ & blending prism, Hicoflex® for discharging API from Isolator & charging into PMA 150, IBC filling station at discharge of FBP, Post Hoist, Buck® Valve on Courtoy™ Tablet compression, IBC wash station, WIP drain frame.
- Tablet compression machine MODUL™ P with HC ECM

Project: Ranbaxy - Oncology solid dosage formulations;

- Single Pot Processor – UltimaPro™ 75 & UltimaPro™ 10
- Material Handling Solution: IBC with Buck valve, Hicoflex® for discharging API from Isolator & charging into Single Pot Processor, IBC filling station at discharge of Single Pot Processor, Post Hoist Blender, Post Hoist, Buck® Valve on Courtoy Tablet compression m/c, IBC wash station, WIP drain frame.
- GEA Courtoy: Tablet compression machine MODUL™ P with wash off line ECM

Conclusion

The design of a tableting line able to handle potent APIs in a safe way requires an in depth understanding of the required level of protection. Here the specifics of the API, the dilution with excipients, the containment performance of the equipment and the frequency of operation are the key parameters which are linked by complex interrelations.

Based on the understanding of the above GEA Pharma Systems has the proven ability of creating out of its world class technical solutions a most appropriate production line.

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