High Containment in Tablet Compression

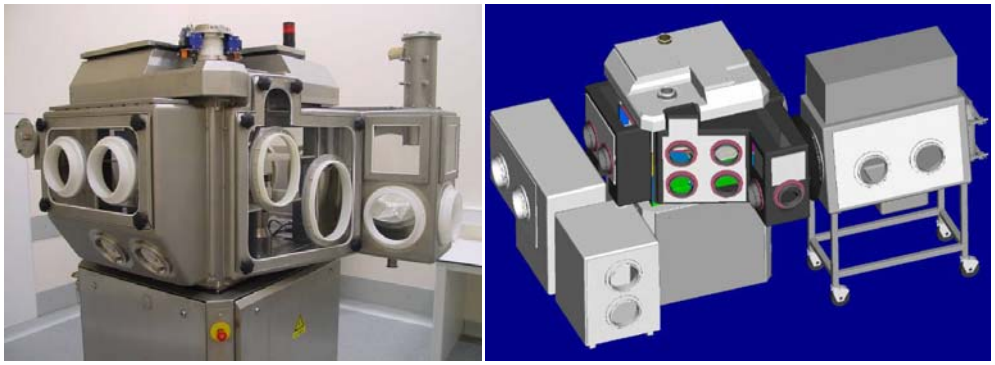
1. Introduction

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.

2. History

Various attempts have been made to address these issues.
The most radical approach is to put the entire press into an isolator.
Courtoy built such an isolated press as early as 1998 (shown in Fig 1).



1. Press in Isolator

Containment levels of down to 0,1µg/m³ could be achieved. The main problem of an isolator based system is the handling, with complete product change-over taking up to 16 hours in the case of the system shown in Fig 1.

In order to eliminate this drawback, a fundamentally different machine concept was developed, whereby the powder containment is performed “at the source”. In 2002, Courtoy introduced the MODUL™ concept. Fig 2 shows the MODUL™ S with its ECM highlighted.

2. MODUL™ S with ECM

3. The ECM Concept

The key feature of the MODUL™ concept is the Exchangeable Compression Module (ECM). The ECM is a completely sealed box; it contains all product-contacting parts and is easy to remove from the machine. It is shown in more detail in Fig 3.

3. ECM - Exchangeable Compression Module

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.

The ECM is also available in a WOL (Wash off Line) execution, which means that it can be connected to a special wash skid, enabling an automatic wash-down without any need to open the ECM or to take out any part, such as e.g. punches.

The WOL concept has significant advantages over a WIP or CIP concept:

- Less consumption of water and detergent,
- Shorter machine downtime,
- No risk of contaminating the electromechanical parts of the machine in case a water seal fails due to damage or wear.

As highlighted in the introduction, during operation, raw materials constantly flow into the tablet press and finished tablets leave at the same time. These flows must also be handled in a contained manner. The best solution for loading is to dock the raw material container via a split butterfly valve. The active part of the valve needs to be executed as a “quick release” version. The tube guiding the raw material from the valve to the ECM is connected with the ECM via LDPE lay-flat tubing. This LDPE can be heat-sealed and cut for dismantling the powder in-feed assembly, as shown in Fig 4.

4. Heat-sealing and cutting of lay-flat tubing

Similar principles are applied to the other interfaces of the ECM, such as the air inlet, the dust extraction and the tablet outlet.

4. The Concept Applied to Check Weigher / Deduster / Metal Checker / Recipients

To take full advantage of the containment performance of the MODUL™ press, the entire tablet production line can be executed in a dust-tight or high-containment version. For this purpose, Courtoy has designed interfaces with down-stream equipment, executed in a contained way. Peripherals available in dust-tight or high-containment execution, in WOL and non-WOL version, include stand-alone dedusters, metal detectors and combined systems, examples of which are shown in Fig 5 and 6. After use they can be disconnected from the tablet press outlet, using the heat-seal and cut principle.

5. High-Containment deduster/metal checker

6. Wash-off-Line deduster/metal checker

For the tablet recipient containers, various contained solutions exist: the Buck Systems™ tablet bag (Fig 7), the continuous liner tablet collector (Fig 8) and conventional containers connected via Hicoflex® (Fig 9). They can be connected with the outlet of the deduster / metal checker unit either via lay-flat tubing or using the Buck® Hicoflex® system.

7. Buck Systems™ Tablet Bag

8. Continuous liner Tablet Collector

9. Hicoflex® container connection

5. Setup

As part of the setup of a high-containment MODUL™, a pressure decay test can be carried out to check the containment prior to starting a batch. For this purpose, a slight negative pressure of at least 2000 Pa is applied to the press. Afterwards, the rising of the pressure inside the press is monitored. If the time for the pressure to rise from a pre-set starting value to a pre-set end value is within the given limits, the press is released for production. If the pressure decay test fails, a helium leak test can be performed in order to identify any problematic area. By performing these tests it is assured that the press has been set up correctly and the containment performance is as required.

6. Cleaning

At the end of a production campaign, the raw material container can be removed in a contained manner taking advantage of its connection via a split butterfly valve. The active valve needs to be in quick-release execution, so the entire product inlet section can be removed from the tablet press in a contained manner after the lay-flat tubing has been heat-sealed and cut. The same applies to the other connections to and from the ECM. When all connections have been secured, the completely closed ECM can be taken out of the press and be deposited on a carrying trolley. If the WOL execution of the ECM has been chosen, it will be washed down automatically after connection to a wash skid. Afterwards, it can be opened in wet state preventing any remaining traces of material from getting airborne. Such traces can easily be removed during final manual rinsing and drying.

The dedusting and metal detection unit is also available in wash-off-line (WOL) execution, enabling the same washing procedure.

7. Case Studies of High-Containment Installations

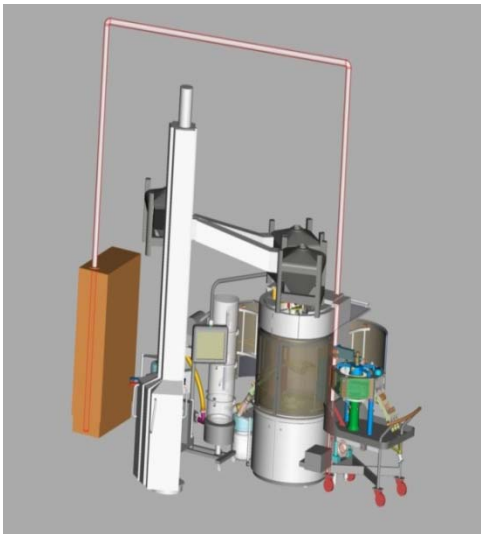
The MODUL™ in itself is a closed system but it needs to be integrated with up- and down-stream equipment to take full advantage of the containment performance. Here some recent installations are shown.

7.1. J&J PRD - Belgium

J&J PRD Belgium, which in 1998 purchased the isolator solution shown above, decided in 2005 to install a MODUL™ S tablet press with WOL-ECM and WOL-peripherals.

The actual setup is shown in Fig 10. It consists of a MODUL™ S with WOL-ECM, a Buck Systems™ post hoist and powder IBCs, a Buck® Valve HC DN100 split butterfly valve in quick-release execution and a Krämer HC WOL deduster + Lock metal-check. An LDPE transparent continuous liner is used to collect good tablets as well as rejected tablets. Samples are taken manually from the same LDPE liner, with the heat-seal and cut technique.

The containment performance of this system has been measured extensively, using air sample and swab test methodology. The results of the tests are discussed in chapter 8.



10. Actual setup at J&J PRD, Belgium

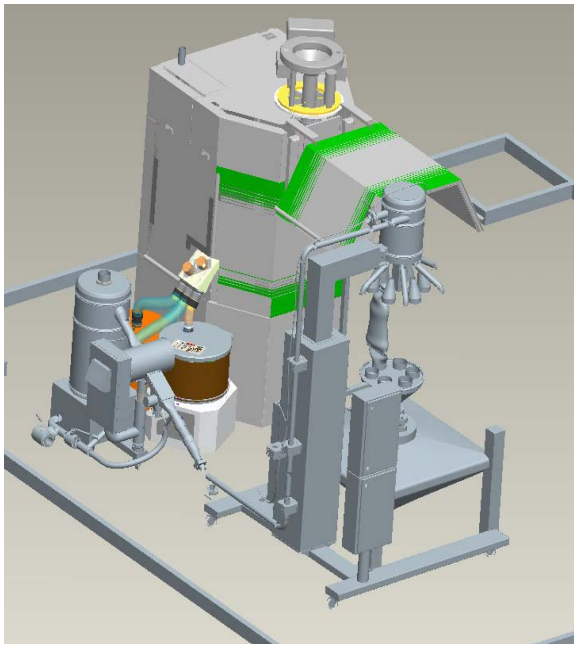
7.2. Servier - Ireland

In 2008, Servier Ireland invested in three high-containment MODUL™ S tablet presses with WOL-ECM, as shown in Fig 11. The raw material comes in IBCs, which are lifted above the press with a post hoist. The material is fed to the press via a split butterfly valve.

A custom-designed high-containment PharmaTechnology system is installed for dedusting and checking for metal particles, while also enabling visual inspection in a buffer before the tablets are released into an IBC.

Accepted tablets are collected in an IBC, which is connected via a SBV, while rejected tablets are taken to a closed bin with spigot.

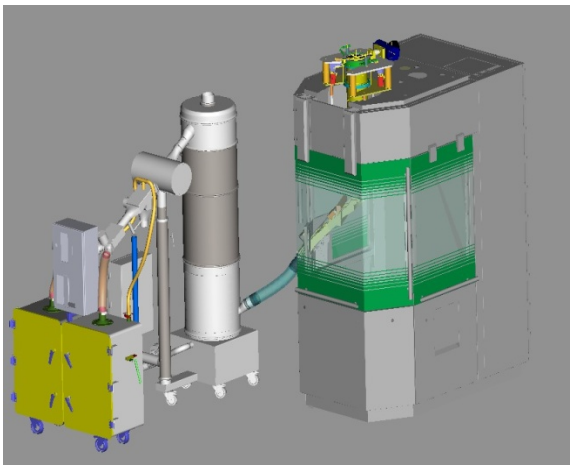
A separate Kraemer-Elektronik washable high-containment Combi-Test performs automatic tablet sampling and measuring for batch reporting and process control.



11. MODUL™ S with WOL-ECM

7.3. Ranbaxy - India

Also in 2008, Ranbaxy India invested in a high-containment MODUL™ P with WOL-ECM, shown in Fig 12. For raw material loading the same principle as in the previous examples is used. At the outlet of the press a PharmaTechnology HC WOL deduster / metal-checker is installed. Tablets are collected in a Hicoflex® SL tablet bag for good tablets (up to 50 litres), while bad tablets are collected in a closed bin with spigot. Samples are taken manually using a continuous liner at the sampling outlet of the press.



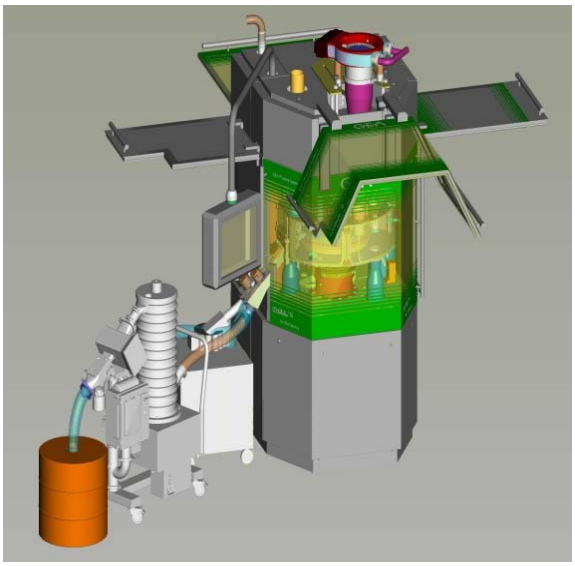
12. MODUL™ P with WOL-ECM

7.4. Haupt Pharma - Germany

In 2008, Haupt Pharma purchased two high-containment MODUL™ S tablet presses with WOL-ECM. The principal setup is shown in Fig 13.

Raw material is loaded into the tablet press through a Buck® MC-200 valve. During production, sample tablets are taken by means of the integrated sample gate on the tablet chute. The tablets are channelled to a Sotax four-parameter tester and the results are downloaded to the Courtoy Multi-Control 4 software for evaluation.

Prior to collection in containers, the tablets are conducted through a Pharma-Flex deduster for dedusting and deburring.



13. MODUL™ S with WOL-ECM

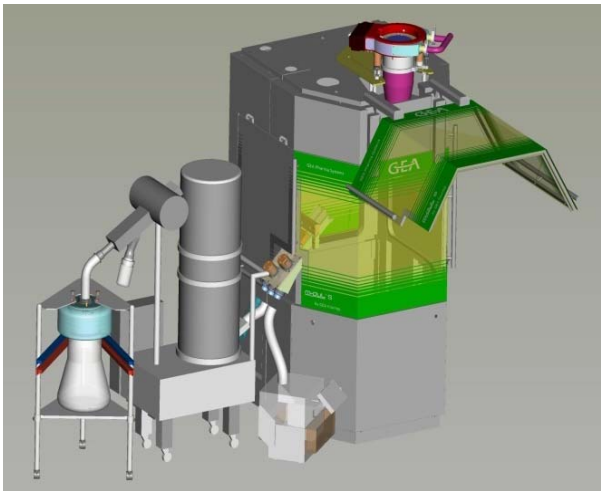
7.5. Teva - Hungary

In 2008, Teva Hungary invested in 2 MODUL™ S presses with WOL-ECM. The set-up is shown in Fig 14.

Granules are loaded into the tablet press through a Buck® MC-200 valve.

The production line also includes a PharmaTechnology dust-tight combined deduster / metal-checker, as well as a Kraemer-Elektronik AWS (Automatic Weighing System).

An ILC Dover continuous liner for good tablets is installed, as well as for the collection of bad tablets, at the outlet of the metal-checker.



14. MODUL™ S with WOL-ECM

8. Containment Performance

The containment performance of a MODUL™ has been assessed by the customer whose setup is described in example 7.1.

The tests were carried out according to the ISPE SMEPAC guidelines. For reasons of compressibility of the material, a different formulation was used instead of the standard lactose grade suggested by the guidelines. This formulation consisted of

- 10% micronized Paracetamol,
- 87,5% Prosolv,
- 0,5% Aerosil
- 2% Magnesium Stearate.

For an entire shift, the airborne concentration of Paracetamol was measured. All phases of operating and running the press were tested:

- the docking of the raw material container,
- the setup of the compression parameters,
- the routine production,
- the removal of individual bags of tablets produced,
- the preparations for cleaning,
- the removal of the ECM,
- the automatic washing of the ECM,
- the manual cleaning of last remaining traces.

Test results:

a) Based on measurement of instantaneous airborne concentration levels, a safe and conservative estimation is that the C-ECM can handle a formulation with up to 10% API concentration, whereby the API OEL is lower than or equal to 10 µg/m³. The WOL-ECM can handle a formulation of up to 10% API, whereby the OEL is lower than or equal to 1 µg/m³.

b) Based on the method of ADI (Acceptable Daily Intake) calculation for a typical MODUL™ installation with WOL-ECM, with peripherals as shown in 7.1. and a typical production sequence, the equivalent LT TWA (Long Term Time Weighted Average) airborne concentration was 88 ng/m³ (or 0,088 µg/m³) for the above formulation with 10% API. This indicates a containment level that is more than adequate for the majority of potent pharmaceutical compounds.

9. Conclusion

Customers are advised to consult with the containment experts from GEA Pharma Systems in the early stages of their tableting project, as a large number of input parameters - such as the potency of the API, the dilution ratio with excipients, the number of operations, the duration of production runs, the presence of operators and the cleaning philosophy - influence the containment requirements of a tablet compression suite.

More about GEA Courtoy

GEA Pharma Systems offers a wide selection of highly innovative and reliable tablet presses for both **pharmaceutical** and **industrial** applications, using GEA Courtoy rotary tablet compression technologies.

GEA Courtoy has been at the forefront of tablet compression innovation since introducing its first rotary press in 1928. Responding to the increasing demand for high-speed tableting machines, GEA Courtoy has established itself as a highly respected supplier of rotary tablet presses.

Since its acquisition by the GEA Group in 1999, GEA Courtoy has been able to expand its worldwide market share and to enhance its position as the true innovator in tablet compression technology for both single-layer and bi-layers tablet presses.

With the introduction of the ECM-based (Exchangeable Compression Module) **'MODUL™'** rotary tablet press in 2002, Courtoy revolutionized the pharmaceutical industry. The **ECM-technology** ***succeeds in combining productivity, flexibility and safety, all in one*** - setting a new standard for pharmaceutical tablet production!

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