BLACK TO THE FUTURE PLANTS WITH AGILITY

A two-floor facility that incorporates the 'black to white' concept may provide oral solid dosage manufacturers with an effective solution for future demands.

Choosing between a single-floor and multifloor plant design for a new oral solid dosage (OSD) facility is a major decision. When land is expensive it is usually more economical to consider the latter option because of its smaller footprint. The new facility should be laid out for 'future needs,' but without the initial high investment cost and without high modification costs later. A single-floor design simply won't fit such a flexible scenario and a multistorey building might be excessive. A two-floor facility, however, may be an effective compromise, particularly when the second floor can do without good manufacturing practice (GMP) classification: this is the 'black to white' concept for 'agile' solid dosage facilities.

Prepare for the Future

With the capacity planning insecurities involved in a new drug application, the best approach for designing a new OSD facility is to make it suitable for multiproduct manufacturing. A plant designed for flexibility can handle last-minute retractions, new life generics or a sudden increase in sales of certain products. Agility helps with 'future proofing.'

In a multiproduct facility, the quickest product changeover is achieved when the discrete unit operations can work in parallel and independent from one another. This automatically leads to the use of intermediate bulk containers (IBCs) for the transfer of batches, or lots, from one step to the next. Unlike vacuum transfer systems, their discharge capacity, although depending on the model, is medium to very high, which reduces the nonvalue add and cycle times for the operation. The IBCs are cleaned offline and so do not negatively influence changeover times: in Lean terms, better overall equipment effectiveness is achieved.

Capacity Boost

Let's assume that the plant has gone through Lean exercises and 'flow' has been created with minimal waste — as far as the highly regulated pharmaceutical processes allow it — and the incentive to reduce inventory and 'make what has been sold' has reached its boundaries and batch sizes have matched customers' orders. Assuming a further increase in demand for the product, now the time has come to lift the whole production chain to a higher capacity level and bigger batches. This means, however, that the overall stack up of equipment will become higher.

How could the original facility design have anticipated that development? Both the building cost and utility consumption make 'white' (clean room) pharmaceutical production areas very expensive. Creating extra volume in the process cells for future use is an expensive option. The solution can be found in the materials handling floor concept (addressed later).

Single-Floor Operation

Analysing the typical OSD operations that require a clean room environment (dispensing, granulation, drying, blending, compressing, coating and primary packing) it can be concluded that machine height does not largely increase with higher capacities: a 10,000-tablets/min press is not significantly higher than one of half the capacity; if you double the capacity of a coating machine, the height only increases to a limited extent. It is the need to increase the batch size that presents a problem. Single-floor facilities are usually limited to 250-kg batches — if you want to use gravity to feed and empty the various processes. There is insufficient headroom to load a bigger IBC above the processes.

This restriction usually explains why drums and vacuum systems are selected for the transfer of batches from process to process. In traditional set ups (Figure 1)

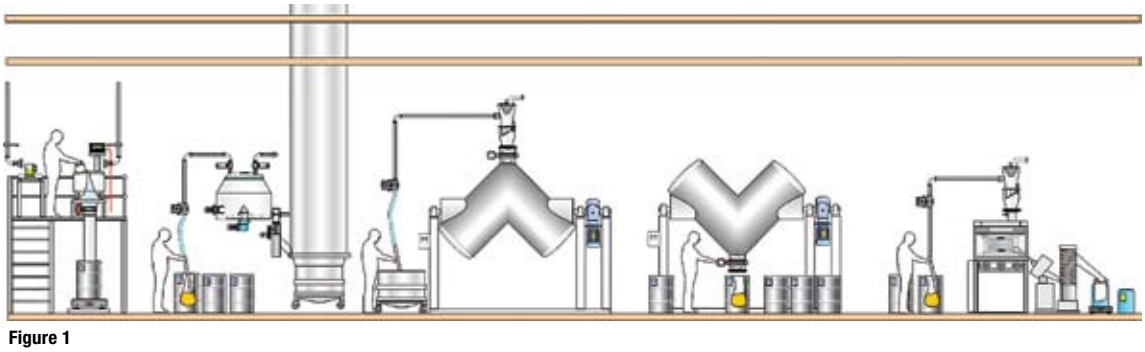

Figure 1: A traditional single-floor facility.

Figure 1

particularly, where the use of large stationary blenders is common practice, there is not enough room to fit a good-sized IBC above or below such machines. This compromises equipment utilization and plant output (blending time is 20 min, but the overall cycle time can be a few hours). Furthermore, all the manual operations, as well as the many 'open' transfers, dramatically increase the risks of error and cross-contamination.

The Non-Lean Way Forward

The existing wet granulation equipment is a difficult factor to consider when batches need to be increased. Allowing these expensive systems to become redundant because of batch capacity is not easily justifiable. A common solution is to collect multiple granulated lots into one (bigger) IBC, which increases the average output of the granulation process, provided the feed and discharge methods are fast (such as when gravity is used). This could be called 'isolated campaigning' in an otherwise synchronized and flowing production line.

A single-floor plant layout that can accommodate future bigger batch size requirements must be designed to include high ceilings. Investing in this option is costly and the overall downtime required for cleaning is significant. Furthermore, in a typical GMP-classified room, the extra air volume needs to be replaced many times per hour. The capital and maintenance costs associated with the many pillar lift-handling units (needed for each gravity discharge point) are not to be neglected either.

The Material Handling Floor

A simple and flexible solution for making the plant fit for larger batches of the future — without investing in high ceilings (costly clean rooms) or dusty equipment that slows down the plant flow (vacuum transfers or manual drum handling) — is the construction of dedicated materials handling floor. Above the process cells, an open area is created where the only 'obstacles' are batch-discharge positions, which are placed directly above the applicable unit operation; for example, granulation, compressing and coating. Using a centrally positioned elevator to, the batches are transported up and brought to the applicable discharge position (Figure 2).

Using a positive pressure in the rooms below and, moreover, implementing state-of-the-art IBC techniques such as 'cone valve' technology or 'split butterfly valve' principles avoids the risk of contamination between discharge positions. The ground-floor suites can now be realized using standard clean room heights without restricting any potential growth in batch sizes. Dispensing also would occur from a second-floor suite down to the receiving area on the ground floor. If wet granulation is used, solutions exist to get the dried product back into the IBC within the same room. There is also proven technology available for cleaning, sampling and venting, as well as for the crucial prevention of segregation (during the powder drop through the floor). Powder blocking phenomena, typically occurring prior to granulation or in direct compression applications, should be fully dealt with by the IBC system.

With regard to blending there is an additional aspect to consider. A prime benefit of an IBC blender compared with a stationary blender (such as a V-blender) is the intrinsic containment of the batch inside the blender chamber, which is in fact the IBC itself. There is no transfer of powder into or from the blender, which assures the absence of blender-room contamination. An IBC blender, therefore, does not have to be placed inside a suite, which in itself saves costs — it can be positioned on the material handling floor (Figure 3) if logistically more beneficial and if the overall ceiling height of the ground floor doesn't allow a bigger IBC blender, such as one of 3 m^3, to be installed.

Many two-floor facilities have been built with a materials handling floor, but only recently have Lean and agile aspects

Figure 2: Materials handling floor (GMP).

Figure 3: Blender at a materials handling floor (GMP).

Figure 4: Materials handling in a technical area.


Figure 2


Figure 3


Figure 4

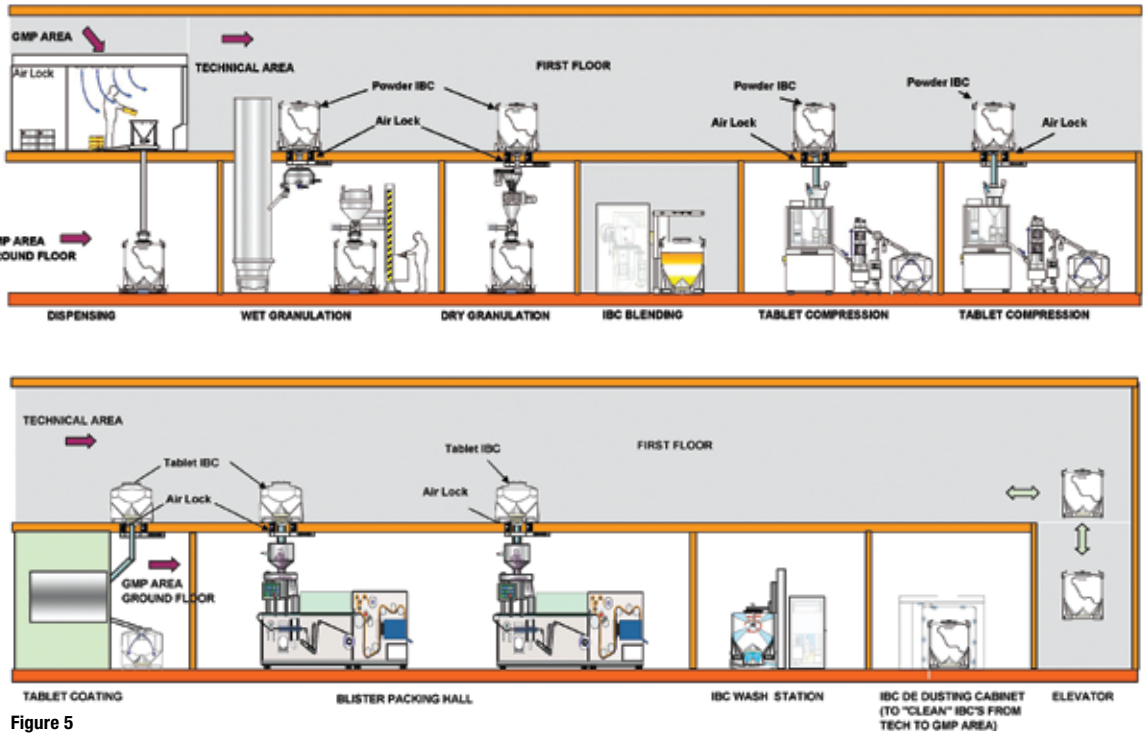

Figure 5: A Lean and agile two-floor OSD facility using a technical area.

Figure 5

of the concept become major factors during plant design evaluation. Yet, the materials handling floor is still tends to be classified as a GMP area, Class 100,000. Why?

Technical 'Black' Area

In compact building designs it is logical and sensible to position utility services directly above — and isolated from — the 'white' GMP process rooms, in a 'technical' or 'black' space. Frequently, these spaces are true floors (as opposed to a space with ducting going through) and are fully accessible. Usually, the total footprint of the technical floor equals the total area of the GMP processes taking place below; yet, the area is often underutilized and so it makes sense to use the free space for the materials handling activity as described above.

The cost benefits of not having to build and operate the second-floor area as a Class 100,000 clean room are obvious; but to be able to use such an area in a proper GMP way, the following points need to be considered:

- IBCs travel between black and white areas. In the direction of black to white, the outer surface of the IBC will need to be cleaned using a dedusting cabinet, similar to that used for cleaning raw material bags and drums coming from outside the facility into the GMP area. This is unnecessary if the IBC is undergoing a full clean because of a product changeover.
- The discharge positions will need to be of a closed design to minimize spillage of positively pressurized clean air into the technical area, which potentially carries dust. This is done with proven, currently available IBC technology.
- To avoid expensive and automated clean-in-place (CIP) systems, the discharge positions will need to be removed for cleaning, but without creating direct contact between the GMP area below and the technical area above. Solutions are available to help with this.
- Powders can never block in the IBC. Opening up the IBC and breaking the containment to assist in the discharge is not an option in a technical area. Cone valve IBC technology will guard against this.
- Further detailed techniques must be applied to create self-venting, mass flow, controlled discharge and proper deceleration to avoid segregation — or demixing — of the blended batches. Also this is available technology.

Summary

A two-floor OSD facility design with a materials handling floor above, has the following main benefits compared with a single-floor plant:

- It is fit for future capacity requirements with limited extra cost, particularly when a technical floor is used; the black to white concept.
- Further investment reduction in the number of pillar lifts and sizes of clean room suites.
- Operational cost savings in cleaning time and HVAC utility consumption of the now smaller clean rooms.

If the floor is defined as 'technical' or 'black,' then additional technology will have to be installed for isolated discharge point cleaning and the dedusting of IBCs travelling from black to white. Extra attention also needs to be given to contained venting, as well as sampling, if required: these techniques are available. The concept of the materials handling floor, particularly when using the black to white concept, places high demands on the IBC system to ensure no blocking, no segregation and containment. A modern cone valve-based IBC system can provide for that. **Pharma**


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