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An efficient replacement of three pieces of equipment with a single one. A case study in a pharmaceutical factory

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This paper describes some critical process changes that occurred in a pharmaceutical plant. The ending section of an Active Pharmaceutical Ingredient (API) extraction process was previously performed by means of three pieces of equipment: mixer+Buchner filter+ dryer. The described change, which imply to conduct the operations in a single piece of equipment, is a very good safety and quality improvement, considering that the solvent is flammable. After the above described crystallization sequence, the filter dryer is rotated in its usual position with the filtering plate on the bottom. Eventually the lot is filtered, dried and finally discharged. In the paper the pilot machine used for the batch trials will be described. The changes respect with the standard piece of equipment will be also explained even with an adequate number of drawings. As a conclusion some of the major improvement in terms of safety and quality will be underlined.

1. The old layout: problems and risks

The steps discussed concern the final section of a complex extraction and concentration process. The whole process requires about 2 weeks. This paper focuses on the two last days when a crystallization and drying occur. Because of the nature of the product, a good crystallization is very difficult and is only complete after several "washing steps" (4 to 5 times). In the previous plant "architecture", about 200 litres of aqueous solution were loaded in an horizontal agitated mixer (see picture 1).
The product was dissolved in this solution. During this step the horizontal mixer was closed and nitrogen purged. Then an alcoholic solution was added while the agitator was running (see picture 2).
From a safety point of view, this operation was protected by means of an oxygen analyzer placed on the mixer vent. A safety interlock switches the agitator off if the threshold of 3% oxygen is exceeded. From the process point of view, the alcohol addition causes the precipitation of a sticky phase containing the product. The consistency of this "rich" phase is similar to a soft rubber (i.e. chewing gum). When the gummy phase was formed, the agitator was stopped and the thick phase was settled (see picture 3). At this point it was necessary to remove the supernatant solution. In the old plant it was done by opening the upper manhole and manually draining the supernatant by means of a pipe connected to a pump (see picture 4). For quality and safety reasons, the area near the upper manhole was ventilated with a Laminar Air Flow (LAF) system. Due to the hand-operated pipe suction, it was difficult to completely remove the

supernatant solution. It was also difficult to avoid removing some product which caused yield loss.

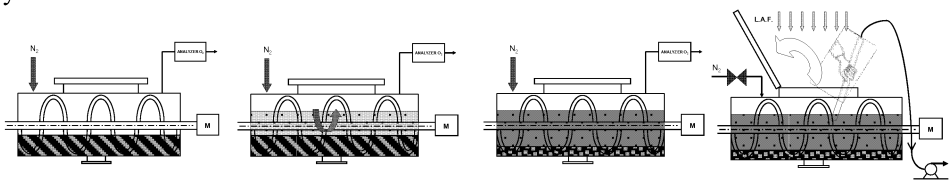

Figure 1-4

After the first supernatant removal, the upper manhole was closed and the nitrogen purging was restored. A second addition of water and alcohol was done while agitating. This operation forced the product to thicken again forming the soft rubber phase. Stopping the agitator allowed the product to settle. At this point a second supernatant removal was necessary. The operations shown in pictures 2, 3 and 4 were repeated in the second “washing step”.

In the crystallization process, there were 4 to 5 “washing steps” as described above. During successive “washing steps” the thick phase tends to loose the consistency of soft rubber and becomes more similar to wet sand. Also the colour of the product changes. During the first “washing step” the thick phase is beige, while at the end it becomes white. These changes signify that a good crystallization has occurred. The wet product was discharged into a Buchner filter by means of the bottom nozzle (see picture 5). In this piece of equipment, a further solvent removal was performed by sucking the solvent through the bottom nozzle with a vacuum pump. A Laminar Air Flow (LAF) was placed above the Buchner filter, similar to the upper manhole. The processes of crystallization and filtering were completed.

For the drying process it was necessary to move the Buchner filter and close the horizontal dryer (see picture 6). The wet product loading was performed manually by means of a shovel through the open front door of the horizontal cylindrical dryer. For quality and safety reasons, a LAF was used. Once inside the equipment, the product was dried by pulling vacuum and “gently” heating to avoid damaging the active molecule. The evaporated solvent was then condensed and recovered. Lastly, the dry product was discharged into drums. Unfortunately, the dryer caused some lumps and the product had to be passed through a mill before being shipped.

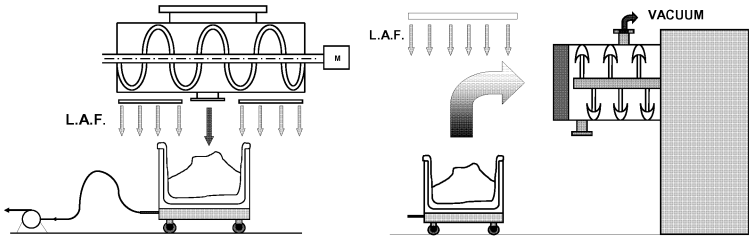

Figure 5-6

2. The improvement of the process

The above process points out some complications due both to the sticky nature of the product and to the need for several “washing steps” before achieving a good crystallization.
Some investigation of more modern multi-function pharmaceutical machines were done. For instance, due to the “chewing gum” consistency of the product, the horizontal centrifuge-dryer had to be rejected as a solution (see picture 7). Also the Filter-Dryer (or Nutsche Filter) was discarded.
The Filter-Dryer is a widely used piece of equipment in the pharmaceutical because of its versatility. A Filter-Dryer is similar to a reactor but has a flat bottom (see picture 8). The bottom is very special because it is equipped with a filtering surface that allows separation of the solid phase in the upper volume while the liquid is drained below.
The recovered liquid flows through a very thin cylindrical volume below the round filtering net (see picture 9). After having filtered a slurry, the Filter-Dryer is also able to perform drying operations by heating and pulling vacuum. This kind of machine is ideal for the pharmaceutical industry because it avoids transferring the wet product from one machine to another.
We now propose to use a Filter-Dryer for our process. Actually, when we load the aqueous product solution into the Filter-Dryer, the liquid solution fills all the volume below the filtering layer and also above the filter until a certain level (again picture 9). The following step is the alcohol solution addition which causes the sticky phase precipitation. Unfortunately in a Filter-Dryer (in this configuration), the product also thickens below the filtering layer and clogs the machine, and causing a real disaster.

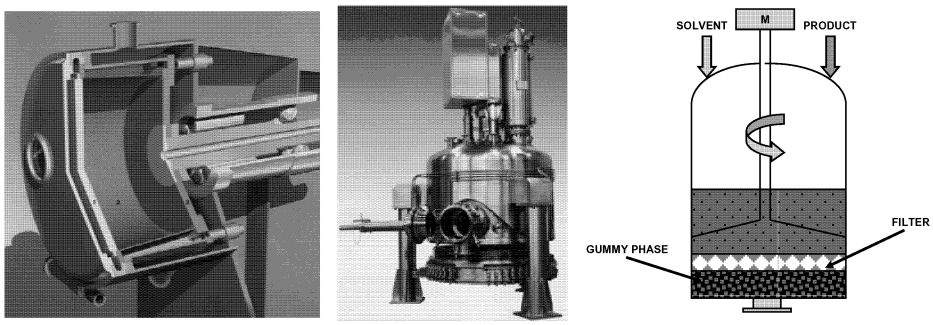

Figure 7-9

The solution was found; it consists of a very special Filter-Dreyer that can be rotated upside down. It doesn’t mean that the “modified” Filter-Dryer is able to spin continuously. Only a 180° rotation is allowed. In the “usual” position, the flat filtering bottom is placed below. In the “upside down” position, the flat filtering surface is placed upward. All the process and utility lines are connected by means of flexible pipes. The described variant of the Filter-Dryer is shown in Picture 10.

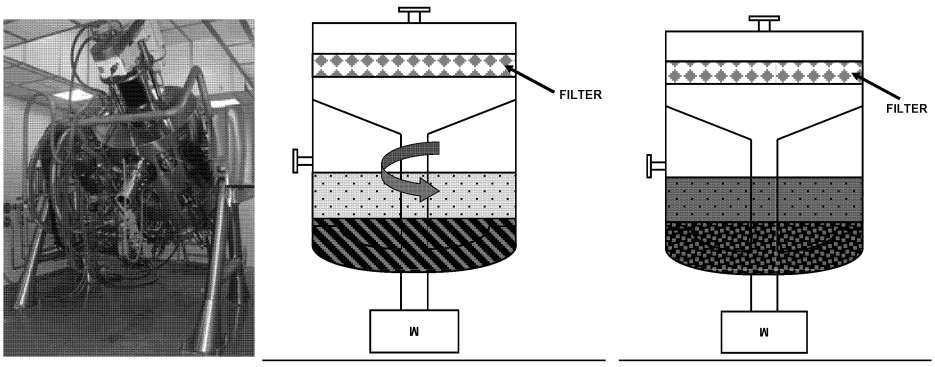

Figure 10-12

Aside from the above described changes (rotation 180° and flexible connections) further adjustments were required. An additional side nozzle had to be placed on the cylindrical shell of the Filter-Dryer in order to allow the supernatant discharge. Also the agitator shape had to be modified to permit agitation in the upside down position. The rotation speed had to be increased to enable a stronger mixing of the gummy phase. The last notable change, concerns the drying step. It is different from the "normal" Filter-Dryer because the drying step is performed with the flat filtering surface upward. This allows use of the filtering net as a separator of potential dust entrainments. This configuration avoids fine product dust to be dragged into the vacuum pump.
The process, as performed in the "modified" Filter-Dreyer, is described in the following part of the paper.
The first step consists of the loading of the aqueous process solution into the Filter-Dryer when the dryer is in the upside down position. The product solution enters into the thin cylindrical volume, included between the filtering cloth and the flat metallic surface, is so avoided. After that the alcohol solution is added, the agitation starts (see picture 11). While the machine is still in the upside down position, the agitator is stopped and the soft gum phase settles (see picture 12). By slowly tilting the Filter-Dryer, it is very easy to remove the supernatant by means of the side nozzle (see picture 13). This critical process step gains a lot of advantages from this modified piece of equipment. First of all it is possible to completely remove the supernatant. Actually, the machine has to be tilted very slowly when the interface is close to the side nozzle (see picture 14). It is possible to avoid some product loss to the supernatant suction pump.

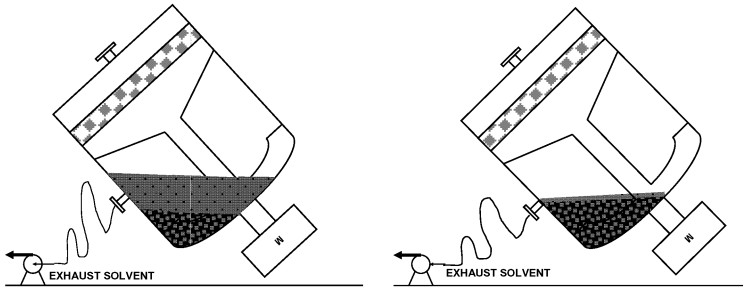

Figure 13-14

The process continues with the other 3-4 “washing steps” as described above. Eventually, the final product crystallizes. It is now possible to avoid the last “careful” supernatant drainage. The Filter-Dreyer is rotated to the “usual” position in which the filtering bottom is placed below (see picture 15). The solvent is drained through the filtering cloth and flows through a bottom nozzle to a suction pump. The solvent removal is made easy by the help of the agitator, which moves the wet powder and scrapes the filtering surface.
Before performing the drying step, the machine is again turned upside down (see picture 16). It is possible to use the filtering cloth to prevent fine product loss, as described above. The drying step is very long when using this kind of machine (almost one day) because it is done very “gently” by pulling vacuum and slightly heating.
The dried active pharmaceutical ingredient is finally discharged into drums by means of a special nozzle (very usual in Filter-Dryers). During this step, the agitator helps the powder discharge (see picture 17).

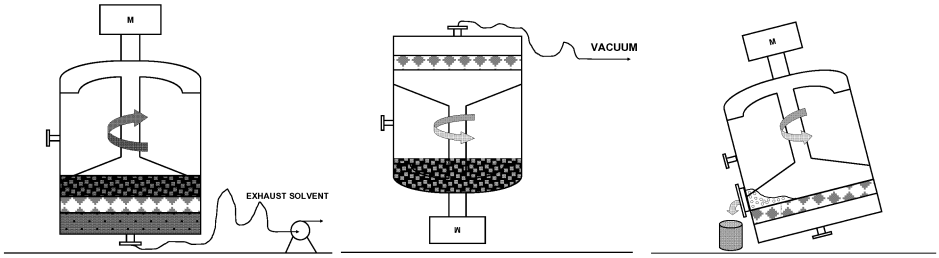

Figure 15-17

The process change was previously tested in a pilot machine (about 25 litres of aqueous solution) by adapting a small size Filter-Dryer. The test results were so encouraging that a series of production “mini batches” were performed.
The advantages of the new technology appear very clear.
In terms of quality:

- The product is more protected because it is no longer transferred between three different pieces of equipment. This is in good agreement with GMP (Good Manufacturing Practices) rules.
- The removed quantities of supernatant solvent are more consistent. Because the process is more standardized, the same quantity of alcoholic liquor are always removed in each “washing step”. The quantity of supernatant removed is no longer dependent on the “manual ability” of the operator.
- The duration of the individual steps is more consistent and predictable.
- The yield is increased because there is no product loss during the supernatant drainage.
- The final particle size distribution of the dried product is finer. The milling step can be avoided.
- The final content of solvent in the product is lower.

In terms of safety and industrial hygiene:

- Several manual supernatant removal operations (i.e. flammable solvent) are avoided.
- Two wet product transfers are avoided: from the horizontal mixer to the Buchner filter and from the Buchner filter to the horizontal dryer. The product always remains in the same machine.
- The nitrogen purging is never interrupted. There are no process steps where the flammable mixture is exposed to a non-inert atmosphere.
- There is a nitrogen saving. Restoring of the nitrogen purging (after the horizontal mixer opening) is no longer required.
- A “standard” purging system (slightly overpressure) is enough. No oxygen analyzer is required.

There are other general advantages. First of all the required area is reduced (one machine instead of three) and the LAF number is reduced from three (horizontal mixer upper manhole; Buchner loading; dryer) to one (product discharge).

3. Conclusion

The facility layout planning problem in chemical and pharmaceutical facilities is concerned with arranging a great number of activities and competences. Our experience shows that layout complexities can be reduced with appreciable improvements in terms of safety and quality. In the case-study presented, there is, unfortunately, a drawback. The piece of equipment used to replace the old three is quite expensive. The cost of the “modified” Filter-Dryer is comparable with other typical machines of the “bulk” pharmaceutical industry (horizontal centrifuges; biconical dryers; special reactors; etc…).
In conclusion, we can say that in the case of very difficult processes, a good solution can be found which combines quality and safety aspects. Of course, all the available technologies must be investigated to reach this result.

3. References

Georgiadis M.C., S. Macchietto, 1996, An MINLP Approach for Safe Process Plant Layout, Industrial & Engineering Chemistry Research Volume: 35, Issue: 4, April 09, pp. 1354-1361

Seung-youp Han A., K. Young-soo, L. Tai-yong , B. TaeSung Yoon. 2000, A framework of concurrent process engineering with agent-based collaborative design strategies and its application on plant layout problem, Computers and Chemical Engineering 24,1673-1679