WIP/CIP and Closed Equipment Systems in the Field of Pharmaceutical Solid Dosage Forms

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Summary:

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In the pharmaceutical industry production equipments of the manufacture of solid dosage forms are cleaned manually, semi- or fully-automated. In order to implement a fully automated cleaning process which meets pharmaceutical (i.e. GMP-) requirements, many conventionally used components must be changed considerably with respect to construction and design. An important aspect is the so-called Total Containment: CIP-ability and Total Containment are interdependent and must be considered equally with the development. The realisation of the Total Containment is an absolute prerequisite for the implementation of this new type of equipment. By the example of a fluid bed system this article describes, how this can be achieved by modifications of conventional equipments and of peripheral devices.

The abbreviations WIP/CIP used in this context are clearly defined. WIP (washing in place) means semi- or fully-automated cleaning with either undefined result of cleaning or with the result that the system is not yet clean according to GMP-requirements. CIP (cleaning in place), on the other hand, stands for the entire process of a fully-automated cleaning to a GMP-conform level, including all factors, which have influence on the cleaning result. This includes the proof that the acceptance criterion of the cleaning validation was achieved.

A comparison study between the manual and fully-automated cleaning shows that by systematic modification of the individual components in connection with a fully-automated cleaning program a higher cleaning grade can be achieved. Furthermore, a statement about the reproducibility of cleaning success can be met.

Keywords

- Equipment systems, containment
- Cleaning in place
- Pharmaceutical solid dosage forms
- Good Manufacturing Practice
- Washing in place

1. Introduction

In past years, increasing attention has been directed to the cleaning of processing systems and the corresponding cleaning validation, both by pharmaceutical companies as well as by monitoring authorities. There are several important reasons for this.
On the one hand, one seeks to lower the risk of cross-contamination for existing products and production lines. And on the other, highly effective materials are becoming increasingly more prevalent in production and manufacturing. For some time now, these materials have placed high demands on cleaning and, in general, have required - in as far as has been possible – a dust-free, closed manufacturing process (e.g., cytostatic agents, hormones, cardiac glycosides, etc.). Exposure of the operating staff, environmental protection and safety aspects provide additional reasons to employ completely closed production lines whenever possible, as is carried out under Total Containment. Additional factors that must be considered are economic aspects as well as the specific requirements for the cleaning validation. Idle times, no matter what their reasons, are unproductive. With the constantly increasing awareness of costs, manual cleaning procedures that are staff-intensive and are time-consuming are being critically compared to automated cleaning procedures that, whenever possible, are carried out at night. Another advantage is that, with automated cleaning in closed systems, fundamentally more aggressive cleaning conditions (detergent types and concentrations, temperatures, pressures, etc.) can be used than those that are employed with traditional methods.

With regard to validation issues, the reproducibility of an automated cleaning has certain advantages when compared to manual hand cleaning. Parameters that are relevant for cleaning tend to be more readily accessible and easier to record and document, thereby facilitating validation. Considering these aspects, an automated cleaning system offers clear advantages.

2. WIP / CIP Terminology

Systems that are very different, even from their stated goal, are frequently lumped together under the same CIP (cleaning in place) designation. The description, CIP Process, already well-ensconced in the liquids sector where it is used in the more narrow sense of the word, has been adapted to use in the solid forms sector.

But which systems in this latter sector actually carry out a CIP process? Installing one or more cleaning nozzles in a processing system, e.g., such as in a fluid bed apparatus that has a conventional construction, may be designated as a CIP system. Nevertheless, it certainly does not compose a system that is clean enough, according to a truly fully-automated, validated cleaning based on GMP standards, that would enable the processing of a formulation with another active agent. Based on these reasons, and especially with conventionally designed systems, the corresponding cleaning systems have been designated *WIP (washing in place) systems*. Here, a good - or even a very good - pre-cleaning is achieved; however, this must always be followed by additional manual cleaning steps. Even when a solid dosage form production system is set up for optimal cleanability and has the corresponding peripheral devices, one can only speak of a system with CIP cleaning in the GMP sense if, in addition to the system design, the respective product, the manufacturing process and the cleaning procedures are also known. Even though in some cases, system manufacturers can claim CIP-compatibility, the following must be considered:
One particular system that has proven to be CIP-compatible for a certain product may not be CIP-compatible for a different product. The system itself can only be laid out for the best possible cleaning, but the actual degree of cleaning achievable must always be determined in each individual case.

3. Design and Technology Requirements

Even while a multitude of processes with correspondingly different processing technology are employed in solid dosage form technology, the critical design principles and design characteristics of the different apparatuses are the same with regard to their cleaning and containment aspects. Flange joints, sensors, unions, viewing ports, filter media with air or gas carrying apparatuses, etc. must be employed throughout the system and product transfer executed. Using fluid bed technology as an example, we aim to demonstrate how the requirements for cleanability and finished product handling can be met and implemented.

3.1. WIP Cleaning

With fluid bed systems having a traditional design, certain components are not suitable, even from the start, for a completely automated, GMP-conforming CIP; therefore, only a WIP process can even be considered.
This will be demonstrated using the example of some of the system parts found in a fluid bed apparatus.

3.1.1. Seals and Gaskets

These are usually found at flange joints (Figs. 1 and 2), sight glasses, sensors, nozzle flanges and blind flanges on nozzle connection pieces, etc. Even here it must be kept in mind that, in addition to the solid ingredient, solutions or suspensions that arise from wet cleaning can also enter into the sealing system. In addition to the actual cleaning (i.e., including the removal of such fluids), the drying of these types of sites is important in order to prevent microbial growth, wherever and whenever possible.

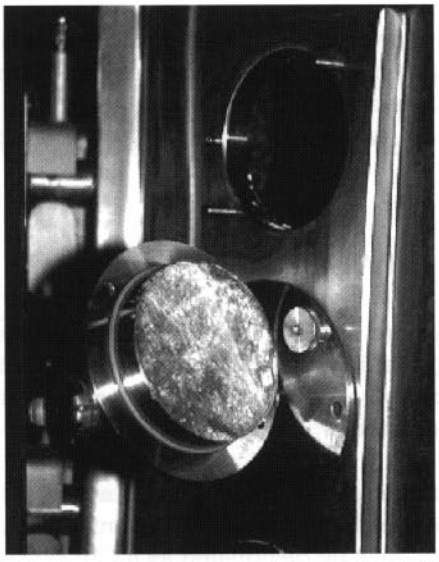

Fig. 1: A conventionally-designed blind flange. When the seal is positioned as shown, the product can accumulate in the gap.

3.1.2. Bottom Screen of the Product Container

A multi-layered design consisting of a supporting floor is frequently used. On top of this is placed a (fine) sieve mesh and a stabilizing construction that eases the strain on the fine sieve. This set-up must be manually dismantled and each part must be individually cleaned in order to remove those particles that have found their way in between the layers (Fig. 3).

Fig. 2: A conventionally-designed flange. With this shape, either the product or the cleaning compound can infiltrate into the seal.

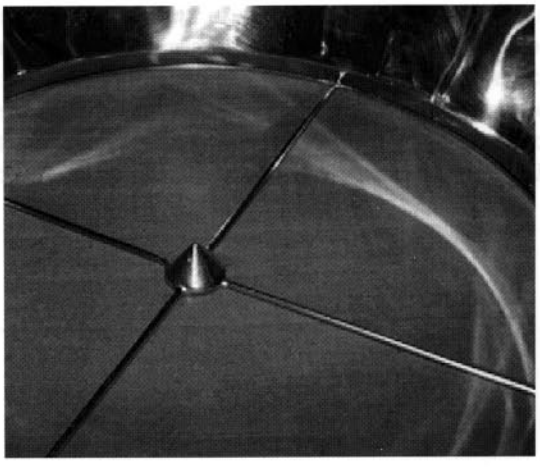

Fig. 3: A conventionally-constructed bottom screen (multi-layer mesh construction).

3.1.3. Sensors

Particularly important to mention in this regard are those instruments used to measure temperature and sites where pressure differences are recorded. Especially when measuring pressure differences, a direct, open connection exists between the measuring site (e.g., directly in the product space) and the pressure transmitter. Cleaning solutions can infiltrate these sites and, therefore, a hand cleaning is almost always necessary.

3.1.4. Product Filters

As a rule, these textile filters are usually in the shape of bag filters that can be shaken or blown out (Figs. 4 and 5). For WIP cleaning, one can first carry out a pre-wash in the system; this helps avoid excessive dust formation during removal from the system. Subsequently, a cleaning in the washing machine takes place while the rest of the system is further cleaned. These filters are very frequently dedicated equipment. An (economically sound) CIP cleanability can usually be excluded because of the types of attachments (such as a clamped flange joint or similar attachment). Specifically, cleaning liquids containing dissolved or suspended agents are transported via capillary forces to sites from which their removal proves most difficult.

Fig. 4: Conventional bag type shaking filters.

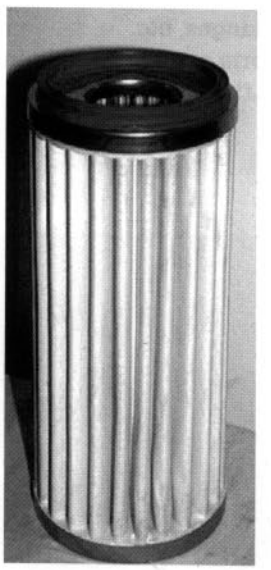

Fig. 5: Conventional pleated filter cartridge with a laminated PTFE membrane.

3.2. CIP Cleaning

In order to achieve the stated goal of having an optimal fluid bed apparatus that can be cleaned without any manual action and which, additionally, adheres to a Total Containment concept, one sees that it is not only the main components that must be critically examined, and if necessary, modified, but also each small detail, no matter how minute, from the charge ports over the sensors and the viewing ports up to the cleaning nozzles themselves. Indeed, for setting up the best possible GMP-conforming CIP for fluid bed systems, the following modifications must be carried out in the various system parts:

3.2.1. Flange Connections, Sealing Systems

To make CIP cleaning possible here, a sealing system was developed which, in the beginning, does not permit the product or the cleaning fluid to enter the flange system at all (Figs. 6 and 7). This is achieved by a correspondingly milled flange in combination with inflatable or mechanically expanding seals which reliably prevent any escape from the inside of the container. The seal is placed in an exposed location, i.e., even though it is in direct contact with the product, it nevertheless guarantees a free inflow and outflow of the cleaning liquids) during CIP cleaning. This is also important with regard to drying, which is only efficient in a free flow-through system.

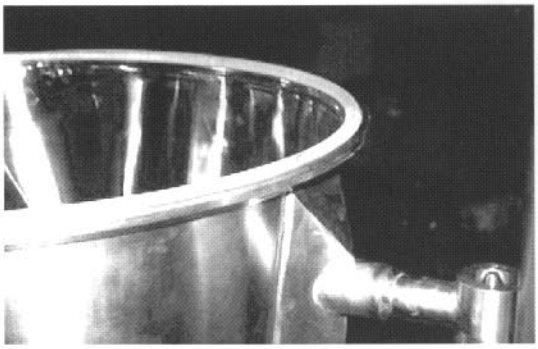

Fig. 6: Example of a transition junction on a CIP-conforming system (Glatt, Binzen).

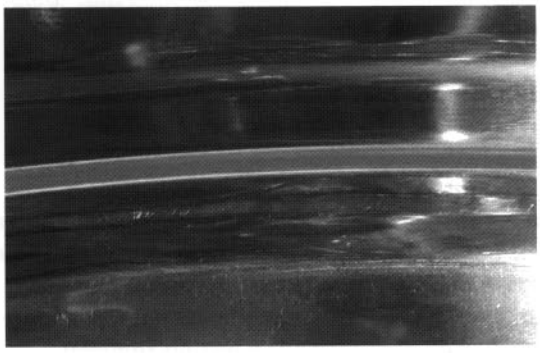

Fig. 7: Inflatable seal, CIP-capable, in the sealed condition (view from the inside of the container) (Glatt, Binzen).

Viewing ports/blind flanges, etc.
Ideally, the viewing ports are solidly built into the system (Figs. 8 and 9). The welded construction thus ensures a smooth and flat surface.

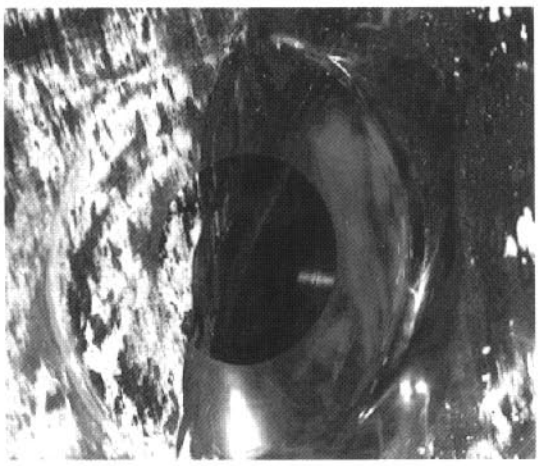

Fig. 8: Welded-in viewing port, CIP-design, after conta-mination (view from the product side) (Glatt, Binzen).

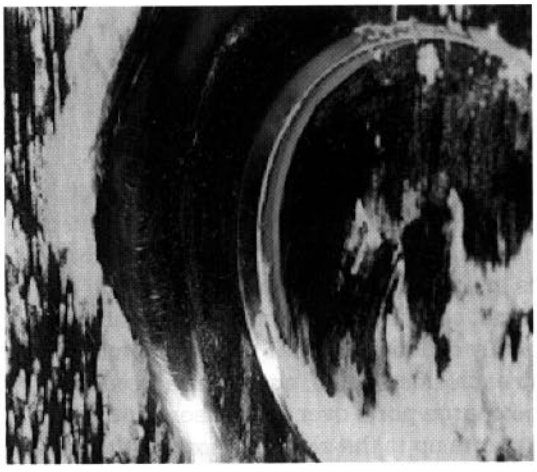

Fig. 9: Viewing port of a conventional design (Glatt, Binzen).

With exchangeable flange systems, the seal should be exposed in direct contact with the product and easily positionable.

Both of these conditions have been fulfilled with a special flange design (O-Plus™-System, Glatt, Binzen; Figs. 10 and 11). Here, the O-ring is hollow and, using a variable collar, can be held in two positions:

a) In an unloaded condition, a twisting or an incorrect positioning of the seal seat is avoided, thereby ensuring a facile installation or dismantling of the flange.
b) In the final sealed state; the O-ring is pressed into the proper position.

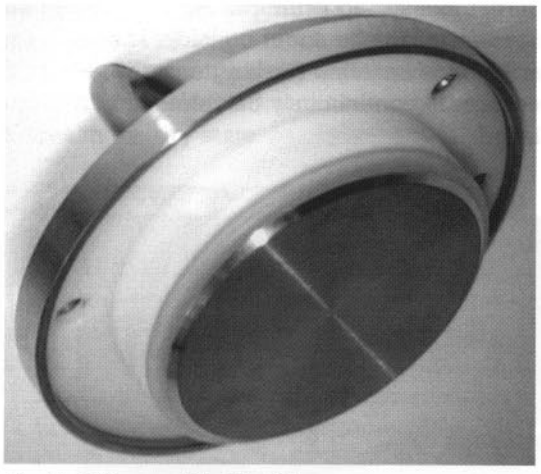

Fig. 10: CIP-compatible blind flange.
(O-Plus™ System, Glatt, Binzen).

Fig. 11: Set-up showing the seal installed,
CIP-compatible design (O-Plus™ System, Glatt, Binzen).

3.2.2. Bottom Screen

Instead of the multi-layered construction having a perforated bottom upon which a fine sieve is placed, a so-called wedge wire sieve is installed (Figs. 12 and 13). This is a single layer leading bottom which is completely accessible from both sides for cleaning. With a defined gap distance (which forms the free surface), stainless steel rods having a triangular cross-sectional shape are arranged parallel to each other. The apex of the triangle thus faces downward so that, when seen from above, the surface is flat and smooth.

Basically, other systems might also be suitable, for example, perforated metal plates with a directed air flow (e.g., screen mesh pierced sheets, such as Conidur® etc.). All floors have the common potential problem that the product can drop into the lower part of the system.

As soon as the leading bottom shows openings that are larger than the smallest particles contained in the product, the product can fall through. Through proper process control, even from the charging stage onwards, this can be reliably prevented as long as the leading bottoms ensure a sufficient pressure difference.

Fig. 12: CIP-compatible wedge wire bottom plate (Glatt, Binzen).

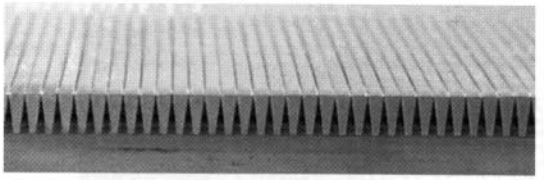

Fig. 13: Cross-section of a wedge wire bottom plate,
CIP-compatible design (Glatt, Binzen).

3.2.3. Sensors

All sensors are installed flush against the wall and do not allow product penetration (Fig. 14). Temperature sensors are welded in, for example, however, they can still be replaced from the outside (Fig. 15). When measuring pressure differences, a completely different measuring principle is employed. An absolute pressure measurement is carried out at the measuring site under consideration. The specially developed sensor is located behind a ceramic pane which is installed flush against the wall and sealed with an O-ring. The difference in the absolute pressures is continuously calculated in the background of the system control and this value is then displayed.

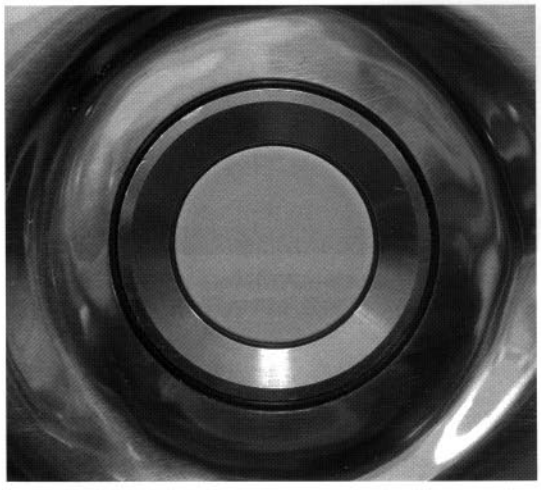

Fig. 14: Pressure sensor, installed in a CIP-compatible construction (Glatt, Binzen).

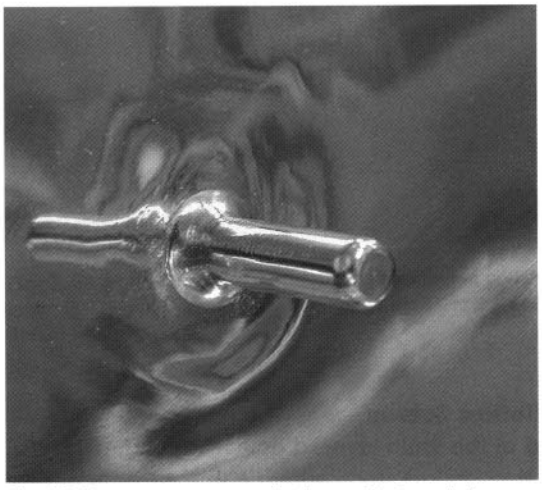

Fig. 15: Temperature sensor in the product container, installed in a CIP-compatible construction (Glatt, Binzen).

3.2.4. CIP-Compatible Filter Cartridge

Stainless steel filters cartridges, having a specific construction and design for ensuring cleanability and long-term stability, are used; this is a most important aspect, especially with regard to wet cleaning. Pleated filter cartridges have a significant disadvantage with respect to product accumulation and a corresponding decrease in the filter surface, accessibility for the cleaning media as well as long-term stability with higher blow-out pressures (Figs. 16, 17 and 18).

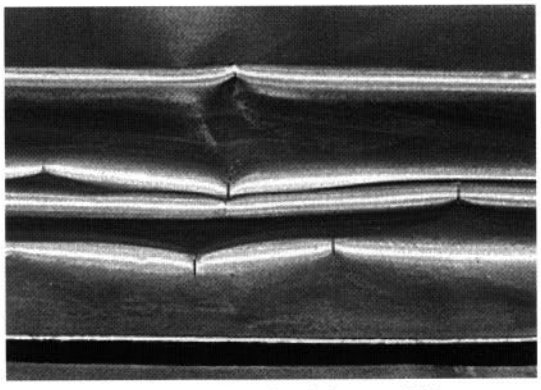

Fig. 16: Example of a pleated stainless steel filter without a corresponding support mesh Demonstrates good cleanability, however, material fatigue arises as a consequence of the blowing out process.

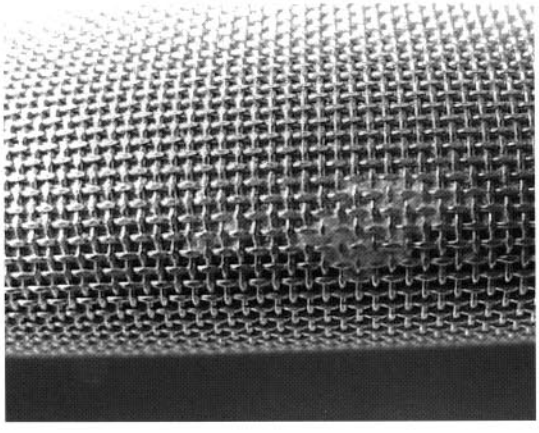

Fig. 17: Example of a pleated stainless steel filter with a corresponding supporting mesh. Demonstrates good mechanical stability, however, product residues are difficult to remove.

Fig. 18: Example of a very dirty pleated filter (spray granulation process). Severe decrease in the filter area on the product side, experiences considerable cleaning problems.

Therefore, a round design was developed where the circumference is fixed (unlike the case with pleated cartridges which experience a significant expansion in their circumference when the pleats are separated out); this round design is extremely stable (Figs. 19 and 20). This design permits one to use a special blow out mechanism that allows considerably higher pressures within the cartridge than those that can be borne by a pleated cartridge, especially with wet cleaning. Due to the capillary forces of the water with wet cleaning, the sieve material forms a considerably higher resistance than it does in the dry state.

Fig. 19: Filter housing, CIP-compatible design (SC™ filters, Glatt, Binzen).

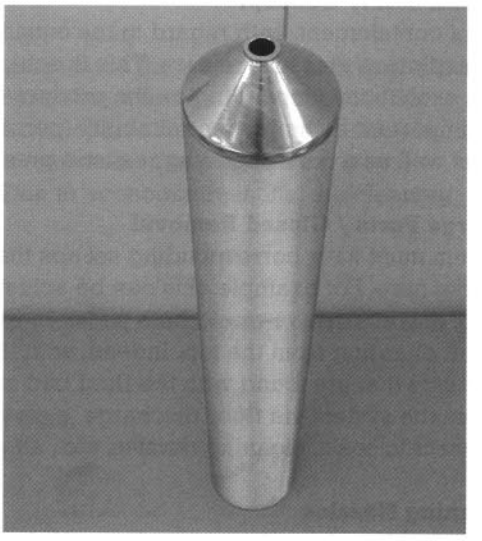

Fig. 20: Stainless steel filter cartridge. CIP-compatible design (SC™ filters, Glatt, Binzen).

Additionally important is that the filtering layer (as needed, up to 2 µm mesh size of the stainless steel sieve mesh) comes to lie in a completely external location and is not covered by an additional outer, coarser supporting membrane (for stabilization purposes), as is usually seen with CIP-compatible plea-ted stainless steel filter cartridges. With a coarser supporting mesh, the product can actually claw its way into the filter and even find its way between the membranes; this poses great difficulty when trying to remove the product.

With regard to the cleaning validation, it should be noted that, here, the usual swab tests fail. Thus product residues present in the filter or supporting mesh cannot be reached. For the cleaning validation, it is recommended that, after cleaning, the cartridge be completely immersed in a corresponding container using the appropriate solvent and that the analysis be made from this (Fig. 21). Likewise, the accumulation of residues should be examined.

Fig. 21: Example of an immersion tank. With the use of a displacement body, the required solvent volume is reduced.

4. Total Containment

Beside the CIP compatibility of a system, a completely closed product handling is another essential part of the total concept. Both aspects complement, respectively, necessitate each other. When compared to conventional systems, changes in the following areas are necessary in order to achieve containment.

4.1. System Safety Concept

As part of containment, with regard to the outside, a completely closed system design can be achieved without explosion pressure release. This is achieved by performing 3 or 10 bar pressure surge resistant executions, depending on the product characteristics (presence of solvent: yes/no).
What is important is the proven reliability (certification by an independent institution) of the chosen design as well as a corresponding realistic pressure test on the finished single system.

4.2. Charge Ports / Closed Removal

The system must have corresponding set-ups that permit a completely closed handling also to be carried out here. For example, this can be achieved by the docking of containers and gravity charging; one alternative would be a possible pneumatic advancement if the housing (-concept) does not permit charging from the top. Indeed, with the pneumatic feeding, the same CIP design requirements that are found with the fluid bed are also necessary here. The product is transported away from the system via floor discharge, a closed side removal or again, pneumatic advancement. With respect to seals, cleaning nozzles, etc., all parts must be designed for fully automated cleaning.

4.3. Cleaning Nozzles

At all relevant locations, the system has self-cleaning cleaning nozzles that remain permanently fixed to the system but which automatically extend during the cleaning process; subsequently, using compressed air, they are dried and then again retract to their original position (flush with the wall) (Figs. 22 and 23). Contrary to the usual WIP process, no manual action before the cleaning is required (opening of the dirty system, inserting the WIP nozzles), so that here, too, work in an enclosed system is possible.

Fig. 22: Extendible cleaning nozzles, CIP-compatible design (Glatt, Binzen).

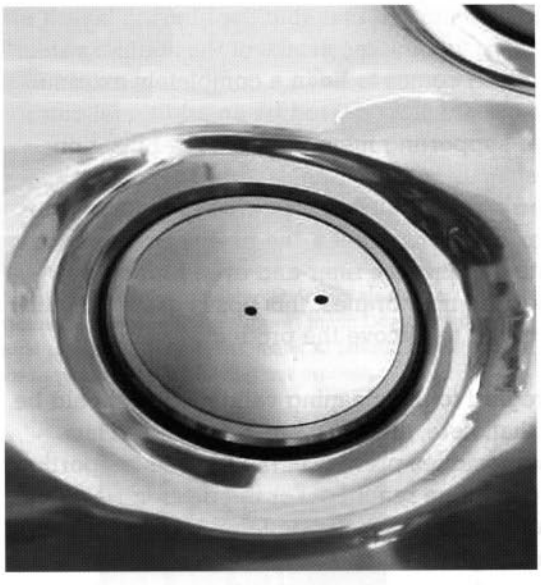

Fig. 23: Extendible cleaning nozzles (in the retracted state); as seen from the inside of the container; CIP-compatible design (Glatt, Binzen).

5. CIP Cleaning Station

For the cleaning itself, there is naturally a corresponding CIP preparation system that is necessary. This system permits the selection of appropriate cleaning parameters and records the required values. Because various system functions (flaps, valves, heating and fan for drying, etc.) must be controlled during cleaning, whenever possible, the CIP program should be managed by the same system control that directs the actual manufacturing process.

The cleaning process itself is determined by the:

- various types of cleaning:
  a) Lost cleaning – usually as a pre-rinse or post-rinse step: Here the water that is brought into the processing system flows directly out of the system after it has had contact with the surface of the system; it is not reused. This ensures that coarse dirt (pre-rinsing step) is removed, as are tenside residues and/or lime-containing water (as post-rinsing steps).
  b) Recirculating cleaning as the main cleaning step. Due to economic reasons, the cleaning medium is pumped in a cycle.

- Type and concentration of detergents:
  Products used include bases, acids, emulsifiers, oxidizing agents, complex-forming agents in appropriate concentrations.

- Temperature, pressure and volume flow of the cleaning fluid.

- Duration of the cleaning.

- Cleaning sequence (of the cleaning and the nozzles employed), etc.

In this manner, the cleaning process can first be optimized, which is a requirement for each validation. The effort involved in the validation of a CIP cleaning should not be underestimated; indeed, it can even be as costly as the process validation itself.

With regard to the costs and the profitability of such a system, lump sum answers cannot be provided; the actual requirement of a Total Containment Concept is, at the moment, much less a question of profitability. Even with products that are not highly toxic, the reduction in cleaning time from between 0.5 to 2 days down to less than 4 hours, with considerably less personnel involvement, can present a most considerable savings potential.

It is also well possible, and even makes sense, to use individual components of the CIP design in a conventional system. Each improvement in procedure and design will also facilitate and speed up the manual cleaning process.

6. Case Study: CIP Cleaning in Comparison to Manual Cleaning

6.1. Introduction

The comparison of these two types of cleaning is currently being examined by A. Schiffmann as part of his dissertation thesis. The results gathered should critically assess the differences in cleaning of a CIP-compatible fluid bed system compared to a conventional fluid bed system.

On both systems, swab and rinse samples were taken after granulation with acetaminophen (paracetamol). The absolute residue of respectively comparable installation parts was examined while considering the variability of the cleaning success.

6.2. Experimental Design

The study was carried out on the following fluid bed apparatus:

GPCG 15 SC (CIP-compatible construction)

- SC metal filter with 10 mm mesh width
- 100 mm wedge wire sieve
- Exclusively fully automated cleaning

GPCG 15 (conventional construction)

This system is a fluid bed apparatus such as is still commonly used in pharmaceutical production.

- Textile shaking filter·
- Bottom screen: PZ mesh between support design and floor plate
- Exclusively manual cleaning

6.3. Contamination

In both systems, a fluid bed granulation using a 33 % active ingredient portion (Acetaminophen) was carried out. After each granulation, a CIP cleaning was performed with the GPCG 15 SC, and with the conventional GPCG 15, a manual cleaning based on a written SOP was undertaken. The tests were similarly repeated twice in both fluid bed apparatuses.

6.4. Cleaning

Conventional GPCG 15

After each batch, a manual cleaning was carried out by the system operator. All three cleanings were carried out by the same system operator. The textile shaking filters were cleaned in a customary washing machine.

CIP-compatible GPCG 15 SC

After each batch, the system was fully automatically cleaned (Tab. 1).

6.5. Sampling

Using a sampling plan, which clearly defined the areas to be sampled, a swab sample and/or rinse sampling was made.

Sampling occurred in the following manner:

a) Swab sample of one defined area (e.g., 10 x 10 cm), representative for a certain system part.

b) Swab sample of a complete system part.

c) Rinsing/immersion of a certain system part in a defined amount of the corresponding solvent.

Cellulose swabs of a defined size were used as the swabs, and were moistened with 1ml methanol. The wiping of the area resulted by successively using two moistened swabs. Subsequently, both swabs were placed together in a test tube.

Tab. 1: CIP-Program.

Step	Sequence	Medium	V (m 3)	T (°C)	t (min)	Remarks
1	Rinsing (lost)	tap water	0.28	15	2.5	pre-cleaning step
2	Washing (recirculated cleaning)	tap water + additive	0.28	80	25	Main cleaning step alkaline[a)]
3	Blowing out	Compressed air	-	-	4	Blowing out the tenside solution from the pipelines
4	Rinsing (lost)	tap water	0.28	15	2.5	Rinsing out the tenside from the system
5	Rinsing (lost)	demineralized water	0.28	20	2.5	"Final rinse"
6	Blowing out	compressed air	-	-	20	Drying the cleaning nozzles
7	Drying	air 1300 m3/h	-	105	25	
Total			1.12		99.5	

Water consumption: 0.84 m3: tap water; 0.28 m3 demineralized water.
a) Mixture of 1% Henkel p3 cosa cip 95 (alkaline) + 1.5 % Henkel p3 cosa cip 92 (alkaline + tenside)

6.6. Analysis

The test tubes were filled with 10 ml methanol and mixed for 15 minutes in the ultrasound bath. The collected samples were then evaluated based on the method described in the USP 23 (Acetaminophen Capsules) for HPLC (UV detection).

6.7. Results

The results obtained were calculated by averaging the three cleaning runs (Tables 2 and 3).

Tab. 2: Agent residue

Sample description	Conventional GPCG 15		GPCG 15 SC (CIP)	
Representative system part	µg/100 cm2	Total residue (mg)	µg/100 cm2	Total residue (mg)
S1 Product container	2.3	90	<0.3[a)]	13.3[a)]
S2 Expansion zone	2.4	922	<0.3[a)]	186[a)]
S3 Seal surface in contact with product	156	538	1.9	10
S4 Lower plenum	354	44250	<0.3[a)]	25[a)]
S5 Sample port	164	115	2.8	1.4
R1 Bottom screen	30.1	289	<1.5[a)]	12.3[a)]
R2 Filter	10.9	2507	<3.9[a)]	1170[a)]
Total residue in the system (surfaces in contact with the product)		48711		1418[b)]

S = Swab samples; R: Rinse samples
a) = For calculating the residue amounts, the detection limit is used.
b) = The amount is calculated from the theoretical amounts. The actual concentration can actually lie well below the number listed.

Table 3: Relative standard deviation (rounded) of the individual measurements

Sample description	Rel. SD (%) Conventional GPCG 15	Rel. SD (%) CIP GPCG 15 SC
S1 Product container	52	- [a]
S2 Expansion zone	39	- [a]
S3 Seal area contacting product	52	23
S4 Lower plenum	87	- [a]
S5 Sample port	137	55
R1 Bottom screen	129	- [a]
R2 Filter	70	- [a]

[a] Measurements below the detection limit.

6.8. Discussion

The following can be concluded from the results obtained:

- The CIP-compatible fluid bed system shows fewer analytically demonstrable contaminated zones than does the manually cleaned system.
- The residue amounts of the individual samples are higher with the conventional construction fluid bed system that with manual cleaning.
- The reproducibility of cleaning success is higher with the CIP-compatible fluid bed system than with manual cleaning.

Other projects are currently investigating the interactions among different groups of formulation components with the various cleaning methods of a technical nature, as well as with regard to the other parameters that determine the cleaning results. The defined goal is, with knowledge of the formulation, to rapidly optimize the cleaning in order to achieve a true CIP process that conforms to GMP.

7. References

Harder, S. W., The Validation of Cleaning Procedures, Pharm. Technol. 8, 29-34 (1984) Mendenhall, D. W., Cleaning Validation, Drug Dev. Ind. Pharm. 15, 2105-2114 (1989)

Baffi, R., A Total Organic Carbon Analysis Method for Validating Cleaning between Products in Biopharmaceutical Manufacturing, J. Parent. Sci. Technol. 45 (1), (1991)

Agalloco, J., Points to consider in the Validation of Equipment Cleaning Procedures, J. Parent. Sci. Technol. 46 (5), (1992)

FDA, Cleaning Validation Mid Atlantic Region Inspection Guide, July 1992

The Rules Governing Medicinal Products in the European Community, Vol. IV, Good Manufacturing Practice for Medicinal Products Commission of the European Communities, January 1992

Code of Federal Regulations, Parts 200 to 299, National Archives and Records Administration, April 1992

FDA, Guide to Inspections of Validation of Cleaning Processes, July 1993

Fourman, G. L., Mullen, M. V., Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations, Pharm. Technol. 17 (4), 54-56 (1993)

Barr, D. B., Crabbs, W. C., Cooper, D., FDA Regulation of Bulk Pharmaceutical Chemical Production, Pharm. Technol. 17 (9), 54-70 (1993)

Zeller, A. O., Cleaning Validation and Residue Limits: A Contribution to Current Discussions, Pharm. Technol. 17 (11), (1993)

LeBlanc, D. A., Danforth, D. D., Smith, J. M., Cleaning Technology for Pharmaceutical Manufacturing, Pharm. Technol. 17 (10), 118-124 (1993)

Jenkins, K. M., Vanderwielen, A. J., Cleaning Validation: An overall Perspective, Pharm. Technol. 18 (4), (1994)

Hwang, R.-C., Kowalski, D. L., Truelove, J. E., Process Design and Data Analysis for Cleaning Validation, Pharm. Technol. 21 (2), 21-25 (1997)

Throm, S., Reinigungsvalidierung, Kommentar des VFA zu den PIC-Empfehlungen zur Reinigungsvalidierung, Pharm. Ind. 59 (8), 664-667 (1997)

Haga, R., Murakawa, S., Ostrove, S., Weiss, S., Cleaning Mechanism Study for BioPharmaceutical Plant Design, Pharm. Engin. 17 (5), 8-21 (1997)

Brutsche, A., Reinigungsvalidierung unter besonderer Berücksichtigung der analytischen Methodenentwicklung und -validierung, Pharm. Ind. 59 (11), 998-1001 (1997) Forsyth, R. J, Haynes, D. V., Cleaning Validation in a Pharmaceutical Research Facility, Pharm. Technol. 22 (9),104-112 (1998)

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