Aerosol Distribution in Filling Processes within Pharmaceutical Isolator Systems

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Key Words

- Pharmaceutical isolator
- pharmaceutical aeroso
- aerosol distribution
- return air system
- particles
- droplets

1. Introduction

Pharmaceutical isolator systems provide a sterile, cleanroom environment for aseptic fill / finish operations [1]. They assure product safety by separating personnel from the aseptic area of production. In the case of highly potent products, this separation also shields the operator from harmful contact with hazardous products, e.g. cytostatic formulations. Product aerosols can be generated by the filling process itself, leakage, spillage and breakup of primary packaging and can therefore result in a contamination of the process area. These product residues from aerosols, spills or splashes may be carried through the transport system, may dry on the machine plate or may be distributed inside the isolator due to the airflow dynamics with a risk of cross-contamination or health risk for the operator during cleaning processes and similar situations. With highly potent products, the contamination paths of process equipment have to be studied in detail and countermeasures have to be identified.

Up to now, there is little knowledge about aerosol distribution and concentration in filling isolator systems. Aerosols may be generated by bubbles of dissolved or trapped air in the product bursting or may be the result of splashes during the filling process, e.g. the liquid stream splashing inside the container.

Therefore, cost-intensive procedures are performed to wash the isolator or expensive preventive processes are installed (e.g. WIP systems in air ducts). Additionally, personal protective equipment is required for employees without confirmation of its necessity.

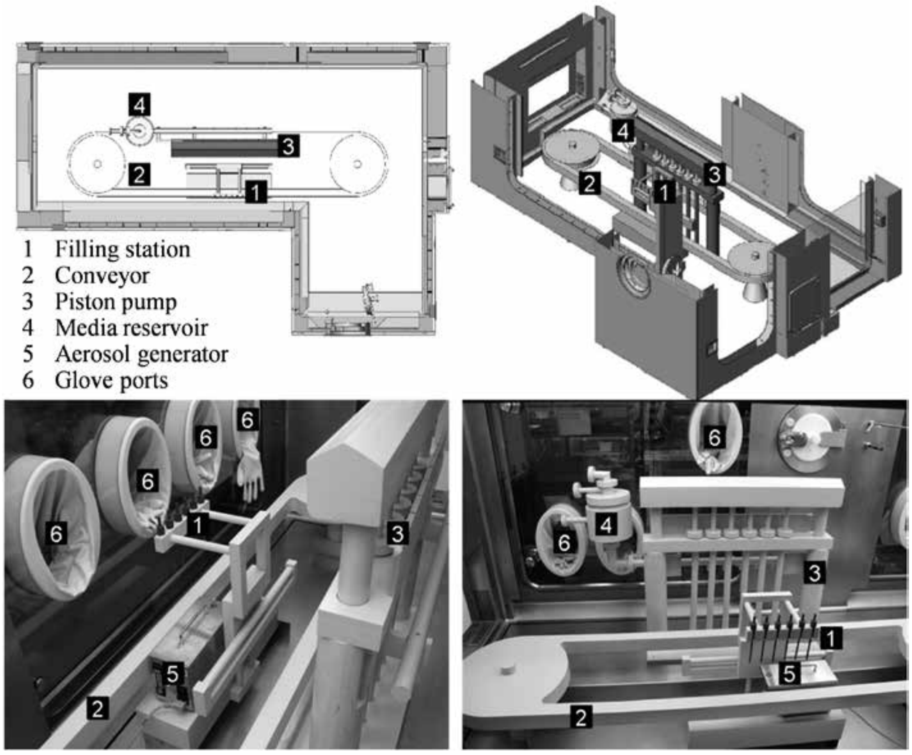

Fig. 1: Experimental set-up with mock-up structure of a filling station (1) with conveyer (2), piston pump (3) and media reservoir (4) in the test isolator system. Position of the aerosol generator (5) is set at the filling station. Access to the production area of the isolator is achieved by glove ports (6).

The goal of this study was to analyze the influences on aerosol formation and to quantify and localize the deposition of contaminants inside of the isolator dependent upon the process parameters and the aerosol source location. These targets could be primarily addressed with numerical [2–4], as well as empirical studies. Due to the complexity of the airflow dynamics inside of an isolator, it was decided to perform an empirical test series in a production size isolator with a surrogate aerosol which could be easily handled and quantitatively analyzed [5].

2. Material and Methods

2.1 Isolator system

Aerosol generation and detection in this study was performed in the production mode of an isolator system with unidirectional airflow (UDF). To simulate production conditions, mock-up equipment of a filling system (No. 1, 3 and 4) and a conveyor (No. 2) were placed into the isolator (Figure 1). Air velocity, under production conditions, in the aseptic process area was determined by a 100 mm diameter vane anemometer (Testo 400, Testo, Germany) and in the return air system by a 16 mm vane anemometer. Three wet air conditions x were established at a temperature of 22 °C: 4.0, 6.0 and 8.0 g H_2O kg^{-1} dry air in order to determine the influence of humidity on formation of an aerosol deposition. This equates to approximately 25 %, 35 % and 50 % relative air humidity (rh), which are in the range of standard air humidities maintained in pharmaceutical isolators.

2.2 Generation of aerosol

The aerosol generation procedures were: generation during production mode and handling failure (spilling of the aerosol solution). The experiment running times were set at 1 hour and 5 hours. A stock solution ($3.64 \cdot 10^{11}$ particles mL^{-1}) of Fluorescein dyed fluorescent polystyrene particles with a particle diameter of 0.5 µm (Fluoresbrit™ Microparticles, Polyscieneces Inc., Germany) was diluted in demineralized water to obtain a working solution of $1.81 \cdot 10^{9}$ particles mL^{-1} [6]. With this working solution an aerosol was formed using an aerosol generator type ATM 226 (Topas, Germany). The mass flow of the generator was adjusted to 2.0 g h^{-1} with a nozzle of 8.0 mm. The aerosol generator was placed at two locations inside of the isolator with different distances from the return air system (Figure 2a position G1 and G2).

To simulate handling failures such as glass breakage, spilling of product, knocking over of filled containers, etc., a glass vial with 20 ml aerosol solution was poured out at a potential spilling area (Figure 2a).

2.3 Sampling and inspection equipment

Sampling of aerosol deposits in the return air system was performed with glass slides (type Polisine™, Menzel-Gläser, Germany), which were placed at a distance of 300 mm from each other, close to the outer wall of the return air ducts. The sampling positions in the return air system are marked as red dots in Figure 2b. The glass slides were clamped to a metal mesh in the direction of the airflow to avoid air turbulence (Figure 2c). The sampling positions in the aseptic area are marked as white dots in Figure 2a (distance from each other d = 500 mm). The sampling positions in the bottom areas of the return air system are indicated with red dots. Particle detection on the glass slides was performed with a fluorescent microscope (Zeiss, Germany, AxioScope 2 with source of fluorescent light HXP 120 C, camera AxioCam 60-C and image processing software AxioVision 4.8) at an excitation wave length of 441 nm. Particles adhered to the glass slides were countable as single spots.

For each glass slide, five representative areas of 1 mm^2 were counted and

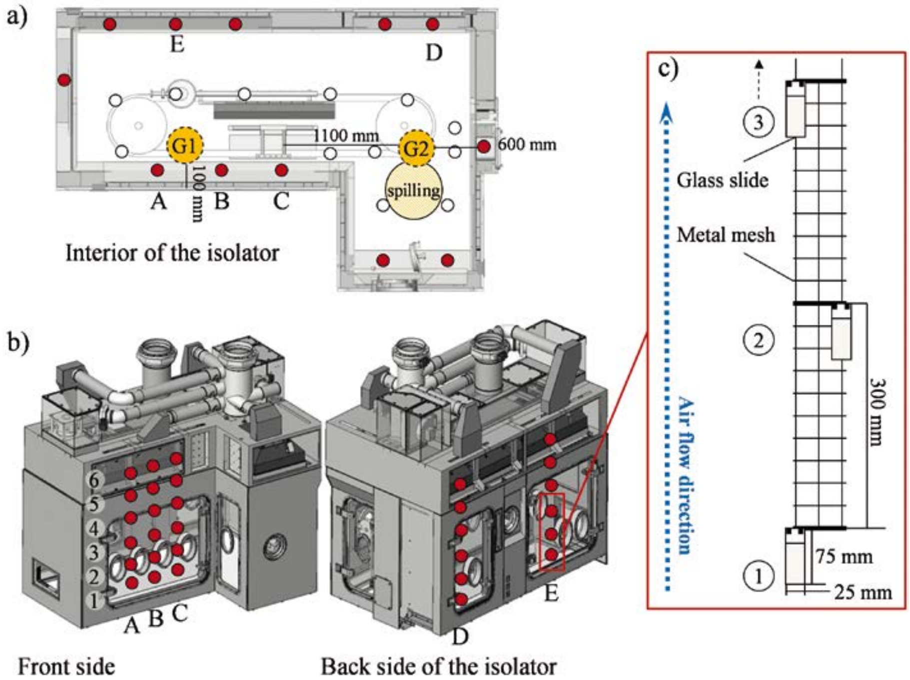

Fig. 2: Experimental set-up (a) with mock-up structure of a filling station and accordant sampling points in the production area of the isolator (white circles), aerosol generator positions (G1 and G2) and spilling area for handling failure. Red marked circles present sampling points at the bottom of the return air system. Figure 2 b) shows sample locations at return air system. Figure c) demonstrates the sample fixation inside the return air duct.

the average value was determined. Particle numbers ≥ 10 mm^{-2} are shown. For some parameter sets, circular droplet-like structures were visible. To mark these effects, particle numbers are indexed with * in the tables.

2.4 Reference cycle

The isolator, equipped with the mock-up parts and aerosol generator (position G1), was run for 5 hours with a 50 % rh without unidirectional air flow (environmental conditions). Particles were found in the production area and in the return air system (Table 1a). They were detected as single particles. Particle sedimentation was very low in the production area of the isolator; < 10 particles mm^{-2}. This may be due to very low gravimetric influences for submicron particles [7]. In the return air area, deposited particles were found in the sampling lines A to D and up to sampling level 3 (equates to a height of approximately 700 mm). In line E no particles were found. The highest amount of particles was found close to the generation source in line A to C.

3. Results and discussion

Air velocity, under production conditions, in the aseptic process area of an isolator is 0.45 m s^{-1} ± 20 %, according to GMP regulations [8]. In the return air ducts the air velocity rises from about 0.7 m s^{-1} at the return air opening near the bottom plate to approximately 7.0 m s^{-1} at

Table 1

Number of deposited aerosol particles in the return air system.

a)

Process mode	Reference cycle 5 h aerosol generation without UDF				
Relative humidity	50%				
Position	A	B	C	D	E
6	-	-	-	-	-
5	-	-	-	-	-
4	-	-	-	-	-
3	19 ± 4	19 ± 3	23 ± 9	12 ± 2	-
2	38 ± 8	24 ± 5	20 ± 4	10 ± 2	-
1	31 ± 11	20 ± 2	16 ± 4	10 ± 2	-

b)

Process mode	1 h production mode with aerosol generation at generation position G1								
Relative humidity	25%			35%			50%		
Position	A	B	C	A	B	C	A	B	C
6	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	16 ± 5	-
2	31* ± 10	-	-	-	29* ± 14	-	53* ± 22	41* ± 11	-
1	18 ± 11	-	-	-	-	-	-	34* ± 14	-

c)

Process mode	5 h production mode with aerosol generation at generation position G1								
Relative humidity	25%			35%			50%		
Position	A	B	C	A	B	C	A	B	C
6	-	-	-	-	-	-	-	-	-
5	-	14 ± 4	-	-	-	-	-	22* ± 5	-
4	-	-	-	-	-	-	-	14* ± 9	-
3	-	56* ± 18	-	15* ± 11	23* ± 12	-	20* ± 7	32* ± 7	-
2	13* ± 5	84* ± 32	-	33* ± 11	47* ± 18	-	56* ± 13	47* ± 16	-
1	-	61* ± 20	-	32* ± 17	30 ± 9	-	-	117* ± 58	-

a) Reference cycle: particle numbers in the return air system with aerosol generation at generator position G1 without unidirectional airflow (UDF)
*b) Production mode with unidirectional air flow for 1 h aerosol generation time n dependency of relative air humidity [%]. Droplet like contours are marked with *.*
*c) Production mode with UDF for 5 h generation time in dependency of relative air humidity [%]. Droplet like contours are marked with *.*

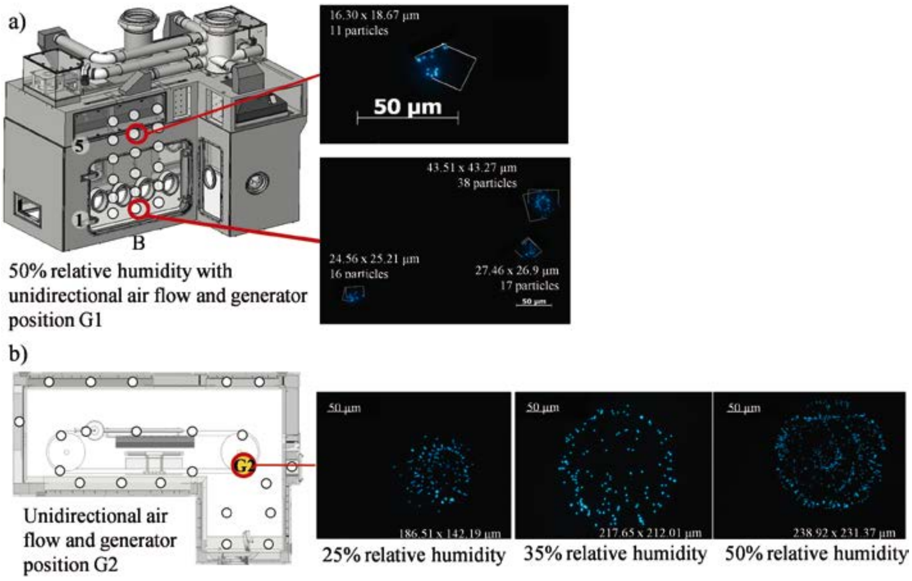

Fig. 3: Droplet size and particle number of aerosol deposition in the return air system, in dependency on distance from the generation source G1. (a); Droplet size in dependency on humidity at generation source G2. (b)

the top of the duct. The air velocity increases because of the reduction in the cross-sectional area of the duct and airflow restrictions, such as glove ports inside the double window.

After each test process, the glass slides were removed and analyzed. Afterwards the isolator was wiped with a wet cleaning cloth. Verification cycles (data not shown) were performed under production conditions without aerosol generation to exclude artifacts / particles from previous process cycles after cleaning. No residual particles were found.

3.1 Generator position G1

For generator positions G1, there was no particle deposition in the aseptic area of the isolator and at the return air areas C, D and E (Figure 2b). Table 1b shows the amount of adhered particles per 1 mm^2 after one hour aerosol generation under process conditions. The obtained high standard deviations from the mean values are a result of the droplet size and therefore the different amount of particles carried per droplet. The aerosol generator generates droplets of varying diameters and the transportation path length varies proportionally to the droplet size, e.g. longer path results in smaller counts. After one hour at 25 % rh, particles and droplets were found at positions A1 and A2. With an increased humidity of 35 % rh particle and droplet deposition occurred at sampling position B2. With a humidity of 50 % rh an increased amount of particles and droplets was found for both lines A (A2) and B (B1-B3).

Table 1c presents the amount of adhered particles and droplets after 5 hours of aerosol generation. In comparison with the results of Table 1b there were many more detected particles and they were widespread above the sampling lines A and B.

With a low relative humidity (25 % rh) in sampling line B, with the shortest distance from the generation source (*d* = 200 mm; Figure 2b), many droplets were found. With 35 % rh in sampling line A (*d* = 300 m) an increased amount of droplets was found. With 50 % rh even at sampling position B4 and B5 particles and droplets were detected. The transportation distance for droplets increased from sampling point B3 to B5 by 600 mm. Furthermore, increased droplet deposition (Figure 3a) and larger droplet size were obtained with higher humidity. As a result more particles were obtained..

In a more humid environment generated droplets may show lower evaporation rates and as a result may have a higher probability of being carried along the transport path and of impacting/adhering to sample surfaces. Therefore the number of droplets is higher in comparison to lower humidities and more droplets are found, even in longer distances. These findings are in accordance with other authors [5], [9] and [10]. Furthermore, due to inertial forces, larger droplets cannot adjust their trajectories to the abruptly changing airflow directions at the bottom of the return air system (≈ 90° at line A1 to C1; Figure 2b) [5]. Therefore, the probability of depositing droplets on the walls increases with increased droplet size, increased deflection angles and reduced return air duct cross-sectional areas.

In comparison with the results of the reference cycle, without unidirectional air flow, no particles were found in line C (d = 750 mm) though the relative air humidity was 50 % rh for both. This could be explained by the influences of the air flow and air velocity near the generation source.

3.2 Generator Position G2

At the aerosol generator location G2, particles were only visible directly next to the generation source (*d* < 50 mm). The aerosol deposited as droplets. Due to agglomerated particles in these droplets, counting was not possible. The influence of humidity on droplet size was also observed (the higher the humidity, the larger the droplets; Figure 3b). The counts very likely resulted from generated aerosol droplets which were too big for transportation by

Table 2

Number of deposited aerosol particles in the return air system with spillage of the aerosol solution and process time of 5 h.

Process mode	5 h production mode 20 ml spilled aerosol solution								
Relative humidity	25%			35%			50%		
Position	A	B	C	A	B	C	A	B	C
6	-	-	15 ± 26	-	-	-	-	-	-
5	-	-	13 ± 12	-	-	-	-	-	-
4	13 ± 13	12 ± 13	18 ± 24	-	-	-	-	-	-
3	22 ± 20	13 ± 11	34 ± 34	-	-	-	-	-	-
2	17 ± 19	23 ± 24	13 ± 19	-	-	-	-	-	-
1	10 ± 5	16 ± 13	42 ± 44	-	-	-	-	-	-

production mode with UDF.

the air flow, therefore they were deposited near the generation source due to gravimetric and inertial forces.

3.3 Spillage

Spillage at the spilling area resulted in a pool of particle suspension on the machine table. During the 5 hour run, aerosol particle deposition occurred only with the lowest humidity of 25 % rh (Table 2). In this case, the airflow was able to transport particles after the pool was dried. The highest amount of particles was found at line C, which was closest to the spilling area. The one hour run as well as higher air humidity (35 % rh, 50 % rh) were not sufficient to achieve drying of the pool. As a consequence no particles were distributed in the isolator or discharged into the return air ducts.

4. Conclusions for design and handling of isolators

The experiments with the aerosol generator in an isolator simulate worst case situations. However, the results may have an impact in design rules and for handling of isolators.

4.1 Design

The distance of the aerosol generation source (e.g. filling system) from the extraction point (e.g. return air ducts) should be as short as possible to avoid contamination of the aseptic area; however, cleaning of the extraction system becomes mandatory. Direct extraction at the point of aerosol generation with a separate device could effectively limit the area to be cleaned. Increased relative air humidity results in larger particles / droplets, which are more likely to be deposited on walls and surfaces. However, larger particles / droplets are easy trapped by filter systems.

4.2 Handling

The aerosol generation area (e.g. filling area) has to be cleaned properly to remove large droplets, which deposit close to the generation source. With spillages of aqueous solutions, as they may occur with handling failures or glass breakage, a relative humidity greater than 35 % rh may be advantageous. This is because evaporation of the spilled solvent and the resulting dispersion of particles from the residue requires a lot more time compared to humidity below 35 % rh. However, to avoid contamination resulting from handling failures, affected areas should be manually cleaned as soon as possible (< 1 hour) and while the spillage is still wet.

5. Summary

Aerosol generation can result in particle deposition in the aseptic area as well as in the return air ducts of an isolator, provided they are not covered with pre-filters. The distance of the extraction systems from the aerosol generation source defines the area to be cleaned. Higher humidity results in higher deposition rates and larger droplets in the return air system.

Also a major source of surface contamination is spilled product. Spilled product has to be removed immediately to prevent drying and the subsequent carry-off of particles. A higher air humidity is recommended to slow the evaporation of the solvent and thereby provide a longer time to clean up the spill and avoid particle dispersion within the isolator.

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