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Safety Issue with Flammable Solvents in Pharmaceutical Production

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In the pharmaceutical production are isolators in use to handle open highly active pharmaceutical compounds. The isolators are the safety barrier to avoid inhalation or skin contact with the highly active substances. From time to time the isolators must be cleaned and disinfected due to GMP and microbiological requirements. Often flammable solvents like ethanol are used for this purpose. Contrary to Deconex® and others, flammable solvents dry without leaving any residue behind. Disinfection is carried out by spraying, wiping or bathing most parts of the equipment, the plant and the room. By spraying flammable solvents, formation of an explosive atmosphere is possible. Swissi simulates evaporation of flammable solvent in an self build isolator under different conditions by spraying the solvent. Normally the equipment and ventilation of an isolator is not designed to prevent explosive atmosphere. Some ignition sources are present every time. Typical electronic equipment like ultrasonic baths and balances but also the electrical installations of the room itself, hot surfaces, mechanical sparks and electrostatic discharges could ignite this atmosphere and endanger people and plant. Some events of exploded isolators are known. Low ventilation can also easily lead to inhalation high above the accepted exposure limits when the isolator is open to the room or exchanges air with it. The experiments will show how the air exchange can be optimized or disinfection can be further optimized, so that an explosive atmosphere can be excluded.

1. Introduction

In the pharmaceutical industry, the isolator technology is increasingly being used to protect the employees during the processing of highly active ingredients. By using isolator technology, employees can waive on personal protective equipment in a substantial part. In the isolators, powders are mainly processed. The manufacturing processes include milling, screening, mixing, weighing and preparing of suspensions, with and without flammable solvents.

The isolators are operated at slight underpressure, suck the supply air through a filter system and release the exhaust air, either completely or partially purified, to the room. In general, some of the air is recirculated.

Today's demands on the production processes are very high. Due to GMP requirements, extensive cleaning of the isolators must be carried out after use. This includes the final disinfection of the isolators. The disinfection is carried out usually with residue-free disinfectants. These include 70 vol% Ethanol and 70 vol% Isopropanol solutions. Other disinfectants such as Deconex® or Chloramin T cannot be used for surfaces with product contact, since they leave residues. In the use of alcohols, however, the high flammability, and ability to explosion must be considered.

The disinfection as an integral part of the cleaning intends to ensure, that biological material, in the form of bacteria, viruses and fungi, is destroyed. From the hygienical point of view, surface disinfection is much more effective than the aerosol-like spraying of alcoholic solution. In hospitals, this has long been practiced like that. In the BGR 206 "Desinfektionsarbeiten im Gesundheitsdienst Juli 1999" the use of 50 g/m^2 for surface disinfection is taken as a basis, without surpassing the Lower Explosive Limit (LEL) of 3.1 vol% and 59 g/m^3 Ethanol, if the room is adequately ventilated by active ventilation, air conditioning or free (natural) ventilation, during the application of alcoholic disinfectants. In addition, the electrical ignition sources must be switched off. If this is not possible, all switching operations have to be interrupted. In large rooms, these measures are sufficient, because dilution of the vapors keeps their concentration well below LEL.

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This paper represents a contribution to show, what using flammable solvents to disinfect isolators and working with flammable solvents in isolators means in terms of explosion protection. For this purpose, various conditions were simulated and underlined with experiments in an isolator model.

2. Evaporation experiments in a model isolator

For the experiments, following setup was chosen:
isolator volume: 0.504 m^3
base area of the isolator: 0.72 m^2
spraying quantity: 50 g/m^2 (70 vol% Ethanol)
air exchange rate: 1, 5 and 10 /h
sprayed surface: 0.2, 0.7, 1.92 and 3.12 m^2
Measuring point was central inside the isolator. Suction point of the ventilation was central at the top of the isolator.

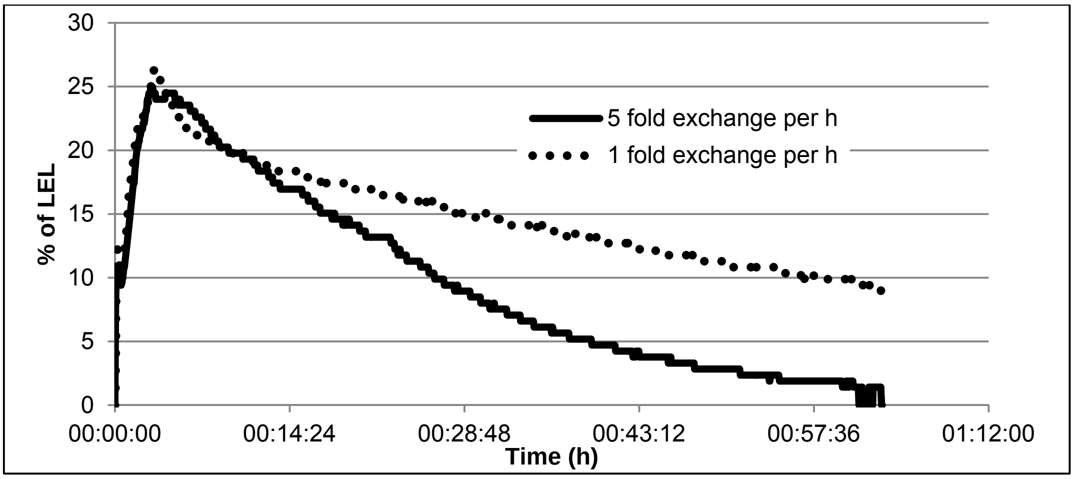

Figure 1: Disinfection in closed isolator with different air exchange rates (wetted area 0.2 m^2, 50 g/m^2)

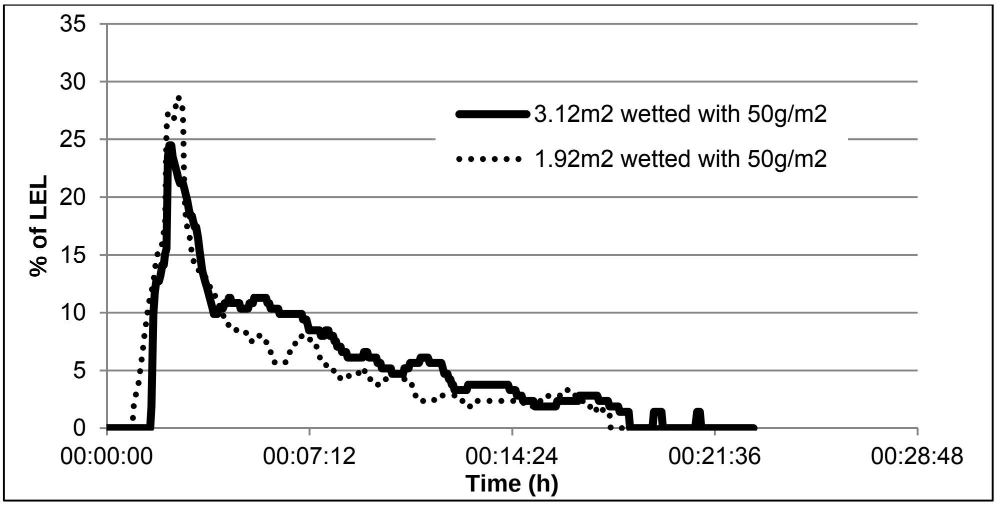

Figure 2: Tests in the open isolator (back wall removed)

The tests in the closed isolators show that the LEL may be exceeded at low air exchange rates and above wetted areas of about 0.5 m^2. Moreover, the evaporation is so fast that the minimum exposure time for effective disinfection is often not fulfilled with a quantity of 50 g ethanol per m^2. Increasing the amount – however – increases the risk of exceeding the LEL.
On the other hand, LEL is not exceeded even with very large wetted area if the vapours are dispersed into the room (5-fold air exchange per hour). This reflects the situation in conventional disinfection processes (e.g. in hospitals, or wash centres in the pharmaceutical production). In these cases the focus should be put rather on exposure risks of employees. (Note that the OEL values of ethanol vapours are in the range of 260 to 1900 mg/m^3, depending on the source)

3. Simulation calculations

In order to evaluate different disinfection scenarios, a simple model was developed.
The models are represented in the figures below.

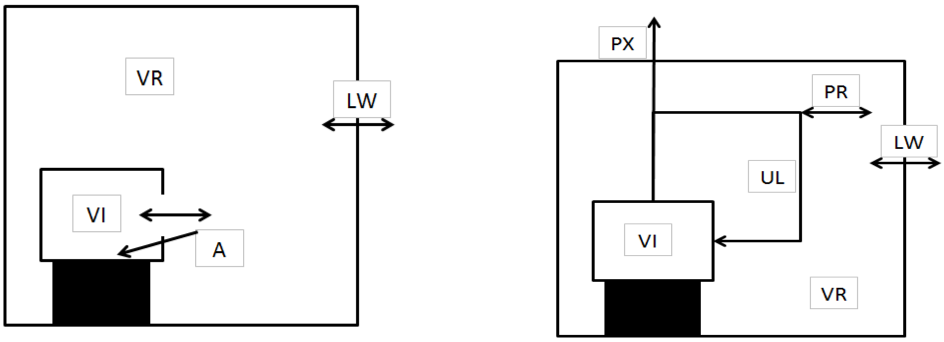

Figure 3: Isolator open to the room (left). Isolator in recirculation mode to the room (right)

room volume = VR [m^2]
air exchange rate in the room = LW [1/h]
isolator volume = VI [m^3]
wetted area = A [m^2]
evaporation rate = E [g/sec·m^2]
disinfection load = S [g/m^2] = 50 g/m^2

room volume = VR [m^2]
air exchange rate in the room = LW [1/h]
isolator volume = VI [m^3]
wetted area = A [m^2]
recirculation rate = UL [m^3/h]
recirculated fraction to the room = PR [%]
exhaust air fraction = PX [%]

The evaporation rate E was determined experimentally to be 0.15 g/sec·m^2

The following operating procedures with typical set ups can be simulated:
- Disinfection in closed isolator with air exchange
- Disinfection in a closed isolator with recirculated fraction to the room
- Disinfection of the open isolator with a defined room air exchange rate
- Open handling / work with flammable solvents in the isolator

3.1 Disinfection in closed isolator without air recirculation (PX = 100%)

Chapter 2 At low air exchange rates, the model shows a good agreement of the maximum vapor concentration, however the decay times are not precisely reflected. This may be due to unprecise or fluctuating air flow.

Chapter 3 At high exchange rates the model is not representative, because turbulence in the isolator leads to uncontrolled effects. At least the maximum concentration calculated by the model is conservative (i.e. on the safe side).

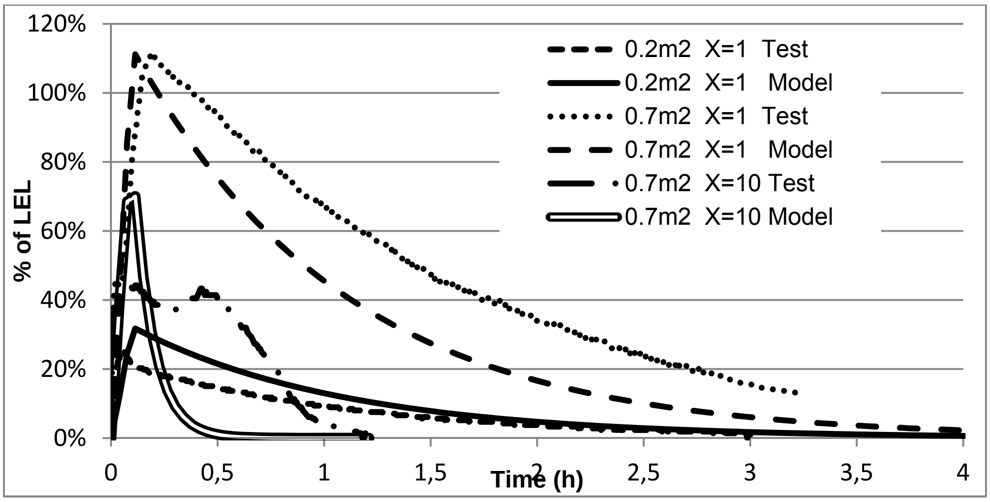

Figure 4: Concentration vs. Time; test and model. X = air exchange rate in the isolator [1/h].

1.1 Disinfection in closed isolator with air recirculation (PX = 20%)

As the application of isolators is mostly related to protection concepts against hazardous or highly active powders, air is often recirculated via high performance filters into the room. As filters do not hold back vapors, the hazards of vapors in the room have also to be considered.

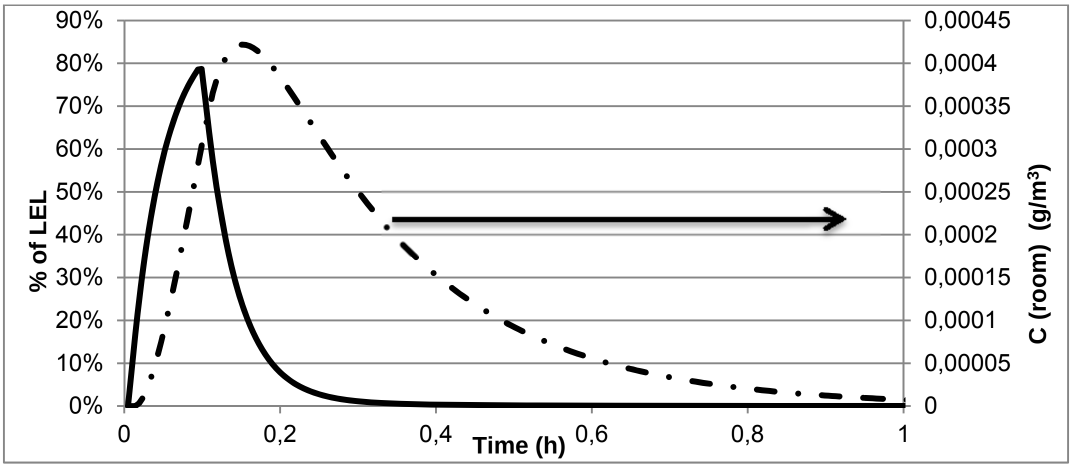

Figure 5: Model of ethanol concentrations in the isolator (continous line) and in the room (broken line). Paramenter: VR: 60 m^3; VI: 0.5 m^3; X(room): 5/h; X(isolator): 10/h; PX: 20 %; PR: 80 %; S: 50 g/m^2; A: 1 m^2

The typical example in Figure 7 shows that the Ethanol concentration in the room is far below OEL. However, in case of spillage of a more hazardous liquid, e.g. Acetonitrile, the hazard of air recirculation must be taken seriously.

2. Ignition source analysis

The experiments and simulations have shown, that a hazardous explosive atmosphere is formed in the isolator. Now the question must be asked, what possible sources of ignition occur in the operation of an isolator according to EN-1127-1. Using an ignition source analysis, this was evaluated and assessed as follows:

Table 1: Ignition source analysis

Ignition source	Assessment
Electrical equipment	Electrical sparks as an ignition source are possible, since electrical equipment, like scales etc., are available during normal operation. During disinfection, the electrical equipment may also be switched on. The ignition source is considered probable.
Hot surfaces	During normal operation, hot surfaces are possible like bearings of rotating parts such as stirrers, the shaft of a sieve or fans as well as welding equipment. During the disinfection these apparatuses are not in operation except for the ventilation. The ignition source is considered unlikely. In assessing the ventilator with a rotating shaft, the ignition source is considered probable.
Mechanical sparks	During normal operation the usage of e.g. mills and sieves can cause mechanically generated sparks. The ignition source is considered probable in this case. During the disinfection these apparatuses are not in operation. The ignition source is considered unlikely. In assessing the fan with rotating wings, the ignition source is considered probable.
Static electricity	Static discharges are possible. The likelihood is, however, considered unlikely, because the substances may be referred to as conductive, if working with alcoholic

Ignition source	Assessment
	disinfectants.
Exothermal reactions, including self ignition	In general, only substances that do not react with one another and are not self-igniting are processed in isolators. The ignition source is considered unlikely.
lightning	The building is equipped with a lightning protection. The ignition source is considered unlikely.
All other sources of ignition are excluded at this point.	

3. Summary

The experiments in the isolator have shown, that it is possible to form a hazardous explosive atmosphere. The main influences in the experiments are, as expected, the amount of ethanol, the sprayed surface and the air exchange rate.

The formation of explosive atmospheres can be prevented by

- limiting the quantity of disinfectant such that even without ventilation the LEL cannot be reached): In this case the LEL may still be exceeded locally.
- applying air exchange rates X $$X > \frac{E \times A}{LEL \times VI}$$
- or air flow rates AF $$AF > \frac{E \times A}{LEL}$$

These formula do not include safety factors, which should be in the order of 4 to 10 (EN 60070-10)

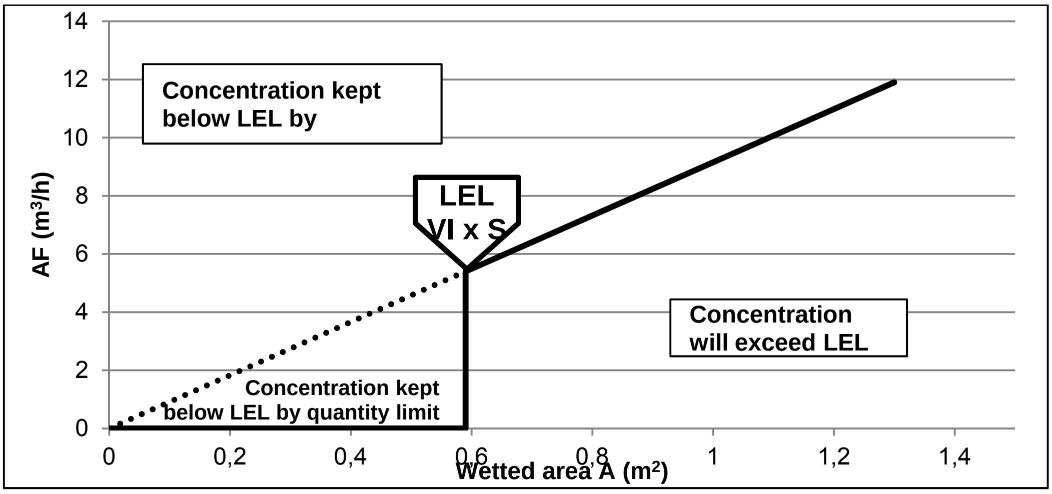

Figure 6: Necessary air flow rate to stay below LEL depending on the size of the wetted surface

In practice, this means that AF/A should be 10 m^3 per hour and per m^2 of wetted area.
However, at such high air flow rates the evaporation is so fast that the required contact time for effective disinfection (15 minutes) is not fulfilled if only 50 g/m^2 of desinfectant is applied. In fact, practice in pharmaceutical industry has also shown, that using spray disinfection, the effective amount of 50 g/m^2 is often exceeded.
Spraying is more dangerous that wiping, since direct evaporation from the aerosol droplets adds to the evaporation from the wetted surface and the probability of the formation of a hazardous explosive atmosphere rises. Since most isolators are designed for the handling of powders, a qualification for Ex zone 2 or 1 is not considered. Thus, the electrical equipment and the exhaust fan remain as an effective ignition source in the isolator. Other potential ignitions sources are filters and / or activated carbon.

4. Conclusion

Disinfecting isolators while they are open lowers the probability of ex-atmosphere formation. However, this way the employee is directly exposed. Favored by spraying, it is very easy to exceed the OEL.
Wherever disinfection with alcoholic solvents is applied, two opposing effects must be considered:
The effectiveness of disinfection is determined by the residence time of the alcohol solution on the surface to be disinfected. This should be about 15 minutes. The experiments and the simulation showed, that at higher air exchange rates, this exposure is not achieved. In these cases, the formation of a hazardous explosive atmosphere is less. At low air exchange rates, the opposite effect can be observed. Disinfection is efficient, but the probability of formation of a hazardous explosive atmosphere is significantly increased.

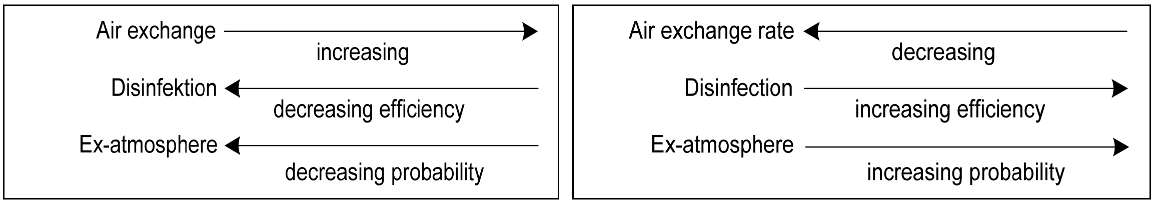

Figure 7: Influence of air exchange rate on disinfection efficiency and probability of ex-atmosphere.

If the avoidance of explosive atmosphere is not possible, the ignition sources have to be identified and avoided

References

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