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PERFORMANCE QUALIFICATION AND OCCUPATIONAL EXPOSURE LIMIT (OEL) FOR ISOLATOR

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ABSTRACT

Isolators are widely used in Pharmaceutical Industries for aseptic compounding applications of sensitive and hazardous substances. Isolator is designed to provide continuous and complete isolation of the inside environment of the isolator from the external room environment (including its operators).Only the gloves provided in isolators or robotic arms are used to compounding or dispensing the product. This ensures that environment is maintained as grade A and contamination-free. Present article can be used to check the isolators when gaskets are changed, glove ports are repaired or new product is taken and to determine the Occupational exposure limit (OEL).

KEY WORDS: OEL: Occupational Exposure Limit.

INTRODUCTION

Determination of OEL (Occupational Exposure Limit) is to identify the amount of drug substance which comes out from the isolator and exposed to the external environment (including its operator) during compounding.

The series of experiments has been performed to verify the isolator for its performance, which are: Light intensity, Air Velocity, Differential pressure across the chamber, Filter integrity test, Temperature & RH monitoring, Viable particle count, Non viable particle count, Recovery test, Air flow pattern, Chamber leak test, Leak test of gloves and Occupational exposure limit determination.

Isolator Description

- The Isolator used in pharmaceutical industries comprise an aseptic processing chamber, the Isolator maintained as Grade A micro-environment in which the various 'open' processing stages of individual aseptic batches can be carried out.
- By design isolators are of two group, one group has the main objective of providing containment for the handling of hazardous materials either aseptically or not. Another group has the main objective of providing a microbiologically controlled environment within which aseptic operations can be carried out.
- Containment isolators operates on negative pressure inside the isolation chamber and most isolators used for aseptic processing works on positive pressure.
- The Isolator designed to stand alone, unit comprising process chamber, transfer hatch, air handling units (complete with fans and HEPA filters) and Suitable sterilizing methods.
- After switching "ON" the Isolator, switch "ON" the lights and blower of isolator and allow to stabilize the differential pressure according to design of isolator.
- Material to be dispense or manufacturing is transferred to pass box with other dispensing tools.
- After attaining the required pressure, material is transferred to the weighing chamber.
- Now the double poly bag covered material is opened and dispensing or compounding of material is done by using glove port.
- After dispensing or compounding the remaining material and empty poly bags are then taken out from the out pass box in intact condition.

Experimental Plan

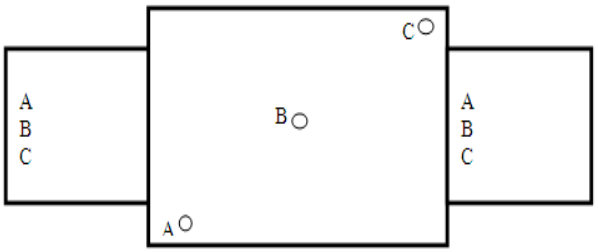
1. Light Intensity
2. Air Velocity
3. Differential pressure across the chamber
4. Filter integrity test
5. Temperature & RH monitoring
6. Viable particle count
7. Non viable particle count
8. Recovery test of Chamber
9. Air flow pattern
10. Chamber leak Test
11. Leak test of gloves
12. Occupational Exposure Limit (OEL) determination

EXPERIMENTAL PROCEDURE

1. Light Intensity Test

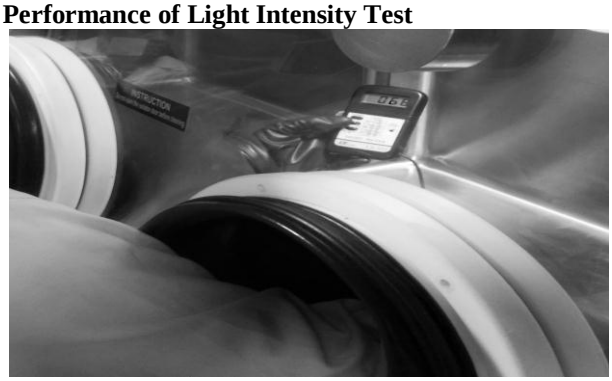
1.1 Light intensity of Isolator chamber shall be verified with calibrated LUX meter (certified by NABL), to be sufficient that provides proper lighting for dispensing and to avoid any discrepancy.

1.2 Light intensity shall be measured at the base of isolator's working place at three location i.e A- Left corner, B- Center & C- Right corner of chamber via Lux meter.



Top view of isolator depicting different Location for light intensity verification.

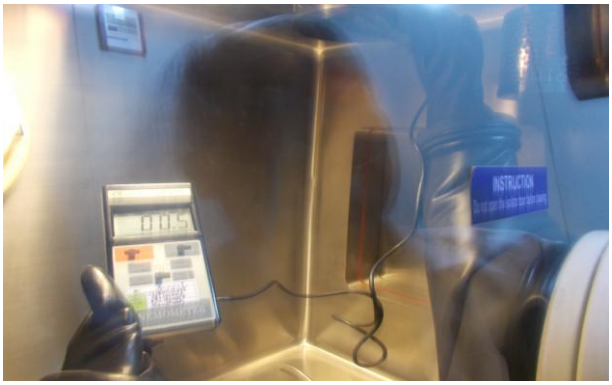
Performance of Light Intensity Test



Pictorial Presentation of Light Intensity Measurement.

2. Air Velocity

Air velocity shall be measured by Calibrated hot wire Anemometer (certified by NABL) in the Chamber at different 5 locations for both Supply duct and Return duct of the Isolator chamber.



Pictorial presentation of Velocity measurement.

2.1 Air Change Rate

2.1.1 Start the Isolator and on Normal running conditions, monitor the airflow into or exhausting from the chamber by using a Hot Wire Anemometer.

2.1.2 From this calculate the volume of air through the chamber and then calculate the Air Change Rate.

2.1.3 Measure the air velocity two inches below the Inlet, at 5 locations (Four corners & One Center) with the Anemometer and record.

2.1.4 Calculate the average velocity of the air coming from supply Inlet.

2.1.5 Calculate the airflow by multiplying the average velocity with the effective filter area.

Air flow = Average Velocity (Ft/Min) x Area of the Air Inlet Filter (Ft^2)

= Ft / Min. x Ft^2

= Ft^3 / Min. or CFM

2.1.6 Calculate the airflow to the entire supply Inlet in the Chamber and add up the values to get the total airflow in the Chamber (CFM)

2.1.7 Calculate the number of air changes per hour by using the formula

Air Changes / hour =

$$\frac{\text{Total air flow in the Chamber (CFM)} \times 60}{\text{Chamber Volume } (Ft^3)}$$

3. Differential Pressure Across The Chamber

The purpose of differential air pressure test across the chamber is to verify the capability of the isolator system to maintain the specified pressure differential between the room and of the inside of chamber of isolator.

3.1 When all doors closed, pressure difference shall be measured and recorded.

3.2 The differential pressure of isolator shall be monitored visually on a mgnehelic gauge at least three times in a shift.

4. Filter Integrity

4.1 Start the isolator and ensure the fan running at normal conditions/ flow rates.

4.2 Position the smoke generator and introduce PAO smoke into the air stream, ahead of

the HEPA filters, at the concentration of 80 – 100 micro gram per liter of air at the filter's designed airflow rating and set the instrument at 100% concentration.

4.3 Scan the downstream side of the filter with an photometer probe.

4.4 The probe should scan the entire filter face and frame at a position about 1 to 2 inches from the face of the filter.

Photograph of filter of Isolator.

5. Temperature & RH monitoring

The purpose of this test is to demonstrate the capability of isolator systems to maintain air temperature and relative humidity levels within the control limits over the time periods.

5.1 Keep the calibrated digital thermo hygrometer in the isolator chamber (at center).

5.2 Measure at least 03 readings for a shift after the stabilization of the temperature and relative humidity.

6. Viable Particulate Count

Viable particulate count shall be taken by two-method i.e. Passive Air Sampling (Settle plate method) and Active air Sampling (Volumetric air sampling) for isolator chamber.

6.1 Passive Air Sampling (By Settle Plate)

6.1.1 Soyabean casein digest agar plates shall be exposed for fungal and bacterial monitoring respectively.

6.1.2 All the plates which shall be incubate, must be pre incubated at 30°C-35°C for 24 hours and one unexposed plate must be kept as a negative control. Keep one agar plate in uncontrolled area. This plate serves as Positive control to check the growth effectiveness of the media.

6.1.3 The lid of the Petri plates shall be placed under the plate so as to incline them towards the flow of air. The Petri plates shall be exposed for 4 hours.

6.1.4 After completion of exposure, these exposed plates shall be transferred to the micro lab.

6.1.5 Incubate the exposed plates at 20.0°C to 25.0°C for 72 hours and count the number of colonies without opening the plates. Further incubate the plates at 30.0°C to 35.0°C for 48 hours and again count the colonies.

6.2 Active Air Sampling

6.2.1 Active Air Sampling shall be done by using the Air sampler.

6.2.2 Switch on the instrument, set the parameters like time and air flow and place the Soyabean casein digest agar media plate carefully to avoid the external contamination.

6.2.3 1000 liters of air shall be sampled by the air sampler. After completion of air sampling, remove the sieve and aseptically place the cover lid on the plate.

6.2.4 Plate shall be recovered after sampling and shall be incubated at 20.0° C to 25.0° C for 72 hours and count the number of colonies without opening the plates. Further incubate the plates at 30.0° C to 35.0° C for 48 hours and again count the colonies.

7. Non Viable Particle count

7.1 Calibrated air borne particle counter shall be used for air borne particle count test.

7.2 This test shall be conducted at rest & dynamic both condition.

7.3 The Isolator chamber must be start before 30 mins of activity to stabilize the chamber.

7.4 Derive the minimum no. of sampling point locations from the formula

Minimum No. of sampling Location = √Area of the chamber in Sq.m

Establishment of single sample volume per location

The single sample volume Vs per location is determined by the formula

$$Vs = \frac{20 \times 1000}{Cn.m}$$

Where,

Vs = Minimum single sample volume per location expressed in liters

Cn.m = is the class limit (number of particles per meter cube)

20 = is the defined number of particles that could be counted if the particle concentration where at the class limit.

8. Recovery test

8.1 Switch on the power of isolator blower from the control panel.

8.2 Open the isolator door for 2 minutes then close it and take the particle count.

8.3 Take the particle count inside the chamber for every minute till the chamber reaches to stable condition(Grade A limit).

8.4 Note the time when particles come within acceptance criteria.

9. Air Flow Pattern test

Airflow pattern test is to confirm either airflow direction or visualization with respect to the design and performance specifications to verify the airflow throughout chamber and the capability of the HEPA Filter unit to limit the dispersion and turbulence of air so as to maintain classified environmental conditions.

9.1 Set the fogger used for creation of smoke of Poly Ethylene glycol (PEG) or suitable substance pointing in the direction of airflow in the center of HEPA filter in flute type pipe in which fog shall be dispersed.

9.2 Smoke is provide for visual indication of the airflow direction and fluctuations due to turbulence

9.3 Verify that the path of smoke is parallel to the airflow.

10. Chamber Leak Test:

Chamber leak test is done to check the integrity of the chamber i.e to determine the chamber is properly sealed or not.

10.1 Persian Blue Sealing check Method

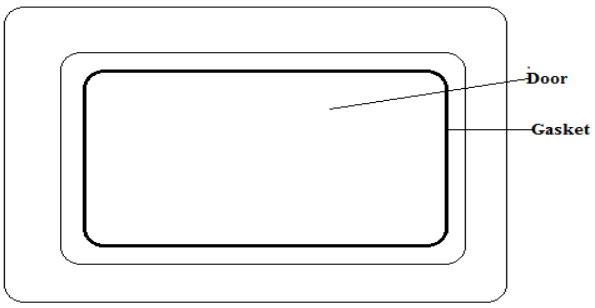
10.1.1 A thin layer of Persian blue shall be applied all over the gasket of the chamber. Chamber shall be then sealed tightly with nut-bolt provided on chamber. (Refer Picture-A).

10.1.2 After opening the chamber door, the door shall be checked to verify presence of Persian blue on door surface. (Refer Picture-B) .

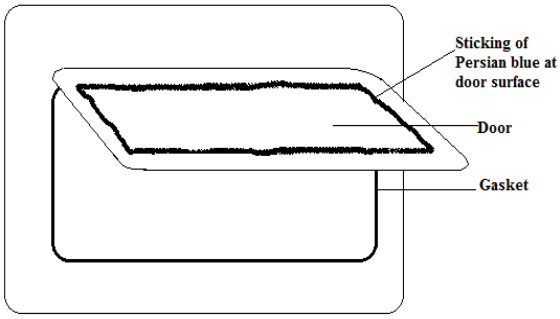
10.1.3 If the Persian blue found to be spread all over the surface of the door where the gasket was touched, it confirms that there is no leakage from the door of chamber.

10.1.4 Put a mark on bolt at which chamber door was sealed for regular sealing purpose.

10.1.5 If Persian blue not found to be spread all over the surface, it means leakage is present. Re perform the sealing check method by means of more tightening of bolt on the door to provide high degree of sticking of door to gasket.



A- Isolator Chamber at Door Closed Condition with Persian blue at gasket



B- Isolator Chamber door front in open condition showing persian blue sticked over the door

11. Leak Test of hand Gloves

Leak test of hand glove is done to verify whether hand glove is capable of acting as a barrier between human and internal environment.

11.1 2 kg pressure of Compressed air shall be supplied to create the positive pressure in the chamber.

11.2 When positive pressure attains in chamber the gloves got swell up.

11.3 To check Integrity of gloves apply Soap solution(T-Pol) on whole glove, specially at all the joints.

11.4 If no air bubble got generated on surface of glove, it means no leakage is present on the glove.

12. Occupational Exposure Limit (OEL) Determination

OEL is determined to verify the amount of the material which is exposed to external environment by the Isolator chamber. Air sampler is used to take the sample from all over the expected joints present in chamber.

Air Sampler Setting (Sample Volume)

To calculate the sample volume to be sucked by the Air sampler, first needs to determine the ACPH of the Room where Isolator has been kept.

For Example

Volume of air to be sampled is determined according to Room ACPH.

Capacity of Dispensing Room AHU is :- 2372 CFM

Room Volume is :- 25.88 m^3

Now for setting up the volume to be sucked by air sampler:-

AHU capacity = 2372 CFM
= 2.372 m^3/min

Air change/hour = 2.372*60
= 142.32 m^3/hr

Volume to be sampled by air sampler
= 142.32/3600
= 0.039m^3/sec

Total Volume scanned from all various location 15 minutes
= 0.039*15*60
= 35.1 m^3

12.1 Determination of OEL (Occupational Exposure Limit)

12.1.1 Take a suitable ingredient which OEL has to be determined (For performance qualification low density powder shall be used).

12.1.2 Take ingredient in isolator and keep into the passbox by means of lock door as per respective SOP.

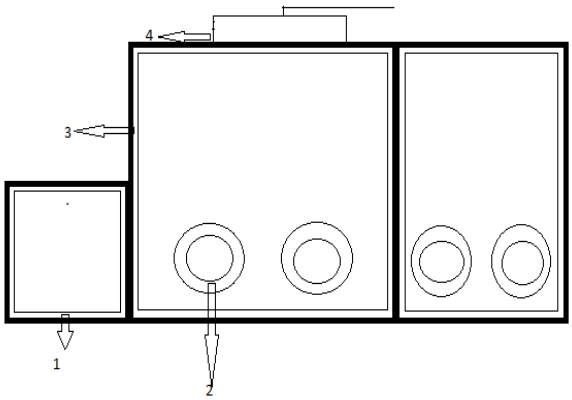
12.1.3 Start the blower to stabilize the isolator by keeping it in static condition for few minutes as per defined procedure (isolator manual) to attain the said differential pressure.

12.1.4 Transfer the material into the chamber by opening door between the chamber and pass box.

12.1.5 Weight the 1 kg of ingredient and transfer it to the double poly bag by means of glove port.

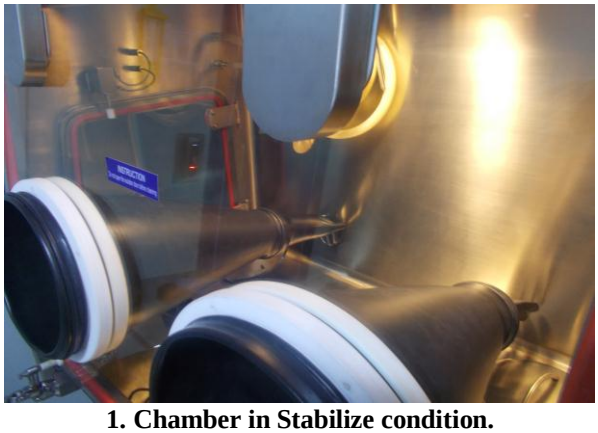
12.1.6 Air sampler having whatman filter of 0.4 micron wetted with 70% of IPA is moved through all the joints of isolator along the inlet pass box window, gloves port and outlet pass box window to take the air sample.

12.1.7 After air sampling the sampled filter paper is properly sealed in a sampling bag and the filters are immediately sent to external laboratory for determination (By LCMS) of amount of ingredient sampled on it to determine the exposed amount of ingredient.



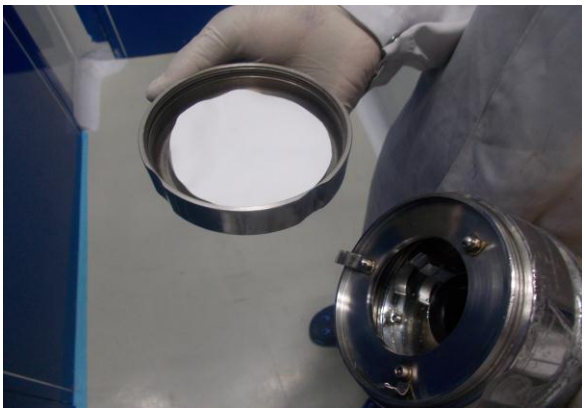
Pictorial presentation of Sampling Location.

*Note: Location 1, 2, 3 and 4 are joint locations for air sampling.



1. Chamber in Stabilize condition.

2. Sample Exposed in Chamber.



3. Air Sampler having whatman filter of 0.4 micron.

4. Air Sampling By Air Sampler.

Acceptance Criteria

S.No.	Test Parameter		Acceptance Criteria
01.	Light Intensity Test		NLT 500 Lux
02.	Air Velocity		As per design and Vendor specification
	Air Changes		
03.	Differential pressure		
04.	Filter integrity		NMT 0.003%
05.	Temperature		NMT 25^0C
	RH		NMT 55%
06.	Viable Particle Count	Active Air Sampling	Less than 1 cfu /m^3
		Settle plate monitoring	Less than 1 cfu/plate
07.	Non Viable Particle Count		Static & Dynamic Condition: 0.5 micron 3520 particle 5.0 micron 20 particle
08.	Recovery test		NMT 15 min
09.	Air flow pattern		As per design data
10.	Chamber Leak Test		No Leakage should be observed
11.	Leak Test of hand Glove		No Leakage should be observed
12.	Determination of Occupational Exposure Limit(OEL)		NMT 0.3 microgram

CONCLUSION

The procedure used for verification of isolator performance and determination of occupational exposure limit will help to:

1. Determine the Occupational exposure limit (amount of drug substance exposed out from isolator)
2. Determine and verify the internal parameters like light intensity, air velocity, chamber leak test and leak test of gloves.

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